(19

Européisches
Pytertamit
Lutepean
Patest Office
Office européen
des proest



(11) EP 1 803 810 A1

(12)

FUROPEAN PATENT APPLICATION

(43) Date of publication: 04.07.2007 Builetin 2007/27

(21) Application number: 06026259.9

(22) Date of filing: 23,02,2001

(84) Designated Contracting States.

MC NUPT SE TR

(51) Int Cl.:

C12N 9/64 (2506.01) A61K 38/16 (2506.01) A61P 37/00 (2006.01) C12N 15/57(2006.01) A61P 35/00(2006.01) A61P 27/00(2006.01) C07K 14/705(2006.01)

A61P 17/02^(2006.01)

 Poindexter, Kurt Matthew Seattle, WA 98103 (US)
 Black, Roy Alvin Seattle, WA 98115 (US)

(74) Representative: Lee, Nicholas John et al Kilburn & Strode,

20 Red Lion Street London WC1R 4PJ (GB)

(30) Priority: 25.02.2000 US 184865 P

(62) Document number(s) of the earlier application(s) in accordance with Art, 76 EPC: 01920133.4 / 1 259 595

AT BE CHICY DE DIK ES FI FRIGBIGRIE IT LILLU

(71) Applicant: IMMUNEX CORPORATION Thousand Oaks, CA 91320-1799 (US)

(72) inventors:

- Fanslow, William C., III
 Normandy Park, WA 98166 (US)
- Cerretti, Douglas Pat Seattle, WA 98133 (US)

Remarks:

This application was filed on 19.12.2006 as a divisional application to the application mentioned under INIO code 62.

•The sequence listing, which is published as annex to the application documents, was filed after the date of filing. The applicant has declared that it does not include matter which goes beyond the content of the application as filed.

(54) Integrin antagonists

(57) The present invention provides methods and compositions for liabiliting the biological activity of integrins, for inhibiting endothetal ceil migration, and for inhibiting anglogenesis, in particular, the invention provides compositions comprising ADAM distritegrin domains and methods for using said compositions. In preferred embodiments the methods and compositions of the invention are used to inhibit angiogenesis and to treat diseases or conditions mediated by angiogenesis.

Description

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of pending U.S. provisional application Serial No. 60/184,865, filled 25 February 2000, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[9002] This invertion relates to methods and compositions that are useful for antagonizing the interaction between integrine and their figands. In particular, the invention relates to the use of ADAM distintegrin domains for antagonizing the interaction between interins and their leannes.

BACKGROUND OF THE INVENTION

A. integrins and Disintegrins

[9003] Integrine are a family of cell surface proteins that mediate adhedion between cells (cell-cell subsolon) and between cells and extracellular matrix proteins (cell-CEM adhesion). Integrine are heterodimate syntures composed of noncovalently bound or and is adounts. In humans, at least fitneen different as subunits and eight different is subunits combine to form Integrins with diverse biological activities and ligand specificities, integrins play important roles in biological processes including embryonic development, platelate laggregation, immune reactions, listue repair and remodaling, bone recorption, and turnor invasion and metastasts. Integrins are, therefore, important targets for therapeutic intervention in burnan disease.

25 [0004] The distinacytine are a family of low molecular weight, actiuble, cysteline-rich peptides which have been isolated from anake venom (reviewed in Niewiarowski et al., Seminars in Hernstology 31(4):289, 1994). The snake venom distingarins typically contain an RGD (Arg 30)-Asp, SEQ ID NO.19) moilt. The RGD moilt if are cognized by many integrins, and is present in several integrin ligancia including fibronectin, vibronectin, and von Wilebrand factor. Disintegrins disrupt normal achesion processes by linbiliting the binding of cell surface integrins to their figancia.

30 [0005] Disintegrin-like domains have been identified in cellular proteins from both invertebrates and vertebrates (see, e.g., Westcamp and Blobel, Proc. Natl. Acad. Sci. USA 91:278, 1994; Wolfsberg er al., Dev. Blot. 169:378, 1995; Alfandari et al., Dev. Blot. 182:314, 1997. Including the ADAM family of transmembrane proteins.

B. ADAMs

0.0

[0006] The ADAMs, which have also been called MDCs, are a family of typs I transmembrane systeine-rich glycoprociens (Weskamp et al., Proc. Natl. Acad. Sci. USA, 91:2748, 1994; Wolfsbarg et al., Dev. Biol. 189:738, 1995). The multidormain structure of the ADAMs typically includes an amino terminal metalloprotoase domain, a disintagrin domain, a systeine-rich region (the region between the disintegrin domain and the transmembrane domain, is transmembrane region, and a cytoplasmic domain. At least 30 ADAM family members have been inderlifed, in a variety of animal spockes. The structure of the ADAMs suggests that they may be involved in a variety of biological processes, including cell anthesion, cell fusion, signal transduction, and proteolysis. Members of the ADAM family make, in tact, been shown to play roles in sperm-egg biological gnd fusion, myotube formation, neurogenesis, and proteolysis.

10007] ADAM-15, also called MDC-15 or metargidin, is the only ADAM itertified to date which contains an RBO motified within its distinction domain and an arranged at Ld Biol. Chem. 273(19)-7345, 1989) have exported that the isolated distingting domain of ADAM-15, expressed in E. coll as a glutatitione S-transforase fusion protein, specifically interacts with $\alpha_{\rm c}\beta_{\rm c}$ integrin and that the interaction is mediated by the RBO bripoptitie sequence. The recombinant fusion protein did not interact with oner integrins tested, including $\alpha_{\rm c}\beta_{\rm c}$ and $\alpha_{\rm c}\beta_{\rm c}$ had the cl. (L. GBI Science 112:75), 1999) have reported that the entire ADAM-15 estracellular domain, expressed as an Fc fusion protein in COS cells, interacts with $\alpha_{\rm c}\beta_{\rm c}$ and $\alpha_{\rm c}\beta_{\rm c}$ integrins on hematopoletic colls and that the interaction is redisided by the RBO therpide sequence. Zhang et al. and Nath et al. commented that the RBO-dependent interaction between ADAM-15 and $\alpha_{\rm c}\beta_{\rm c}$ integrin suggests a role processes such as millipancy and an applicageness.

C. Anglogenesis

[0008] Angiogenesis, the generation of new blood vessels, is a spatially and temporally regulated process in which endothelial and smooth muscle calls proliferate, migrate, and assemble finit tubes. In response to endogenous positive and negative regulatory molecules. Angiogenesis plays important roles in both normal and pathological physiological positions.

[0009] Under normal physiological conditions, angiogenesis is involved in fetal and embryonic development, wound needing, organ regeneration, and female reproductive remodeling processes including formation of the endometrium, corpus luteum, and placenta. Angiogenesis is stringently regulated under normal conditions, especially in adult animals, and perturbation of the regulatory controls can lead to pathological angiogenesis.

[0010] Pathological angiogenesis has been implicated in the manifestation and/or progression of inflammatory diseases, certain eye disorders, and cancer. In particular, several lines of evidence support the concept that anglogenesis is essential for the growth and persistence of solid tumors and their metastases (see, e.g., Folkman, N. Engl. J. Med. 285:1182, 1971; Folkman et al., Nature 339:58, 1989; Kim et al., Nature 362:841, 1993; Hori et al., Cancer Res., 51; 6180, 1991; Zetter, Annu, Rev. Med. 49:407, 1998). The formation of new blood vessels provides a growing tumor with oxygen, nuirients, waste removal, and a conduit by which invasive cells can enter the circulatory system and establish distant metastases. Various classes of anciocenesis inhibitors are presently being developed and tested for the prevention (e.g., treatment of premalignant conditions), intervention (e.g., treatment of small tumors), and regression (e.g., treatment of large turnors) of cancers (see, e.g., Bergers et al., Science 284:808, 1999) and other forms of pathological angiogenesis. Because many steps in the angiogenic process, including endothelial cell migration, proliferation, and morphogenesis require vascular cell adhesion, certain integrin antagonists have been tested as anti-angiogenic agents. [9011] Several integrins are expressed on the surface of cultured endothelial and smooth muscle cells, including $\alpha_s\beta_3$ integrin. The $\alpha_0\beta_0$ integrin is an endothelial cell receptor for von Willebrand factor, fibrin, fibrinogen, and fibronactin, and a marker of angiogenic vascular tissue. Brooks et al. have reported that monoclonal antibodies to c. β4 integrin, as well as cyclic peptide inhibitors, disrupt anglogenesis and that or \$6, antibodies promote tumor regression (Science 264:569, 1994; Cell 79:1157, 1994). These results suggest that m.8., integrin is a useful therapeutic target for diseases characterized by pathological angiogenesis.

[0012] There is great need for additional compositions and methods of antagonizing the interaction between integrins and their ligands. In particular, there is great need for additional compositions and methods of inhibiting amplogenesis for the prevention, perceation, and midigation of disease processes that are deependent upon pathological antiogenesis.

SUMMARY OF THE INVENTION

25

96

[0613] The present invention is based upon the discovery that ADAM disinlegin domains are useful for inhibiting the biological activity of integrins and for inhibiting endotherial cell migration and anglogeness, including the unexpected discovery that these inhibitory activities reside in ADAM disinlegin domains that tack an RGD may.

10014] The Invention is directed to methods of antagonizing the binding of an integrin to its ligands, and thereby inhibiting the biological activity of the integrin, comprising contacting the integrin with an effective amount of an ADAM distinction domain polypepide. The invention is burther disected to methods of inhibiting anotheristic cell inigration and methods of inhibiting anglogenesis comprising administering an effective amount of an ADAM distinction domain polypepide is in the torn of a multimer, preferably a leution expoer multimer or Fic polypepides, in some embodiments the ADAM distinction domain polypepide is in the torn of a multimer, preferably at leution expoer multimer or Fic polypepides, in some embodiments the ADAM distinction domain is from a human ADAM, and preferably from ADAM-8, ADAM-9, ADAM-19, ADAM-19,

[0015] In some preferred embodiments the ADAM disintegrin domain polypeptide comprises an amine acid sequence selected from the group consisting of amine acids 22-264 of SEQ ID NO-22, amine acids 23-39.3 of SEQ ID NO-5. amine acids 23-264 of SEQ ID NO-24, amine acids 23-30.2 of SEQ ID NO-10, amine acids 23-32.0 of SEQ ID NO-11, amine acids 23-32.0 of SEQ ID NO-11, amine acids 23-32.0 of SEQ ID NO-11, amine acids 23-32.0 of SEQ ID NO-12, amine acids 24-30.0 of SEQ ID NO-13, amine acids 24-30.0 of SEQ ID NO-14, amine acids 24

[0016] In some embodiments a therapeutically effective amount of the ADAM distritugin domain is administered to a marryral in need of such treatment. In preferred embodiments the mannral is afficiated with a condition mediated by angiogenesis, an ocular disorder, malignant or metastatic condition, inflammatory disease, osteoprosis and other conditions mediated by accelerated bone resorption, restencesis, inappropriate pitatelet activation, recruitment, or aggregation, thrombosis, or a condition requiring tissue repeat or wound healing. The ADAM distinction domain is, in some embodition.

ments, administered in combination with radiation therapy and/or in combination with one or more additional therapeutic agents.

[0317] The invention also encompasses methods for identifying compounds that modulate integrin biological activity, that modulate the interaction between an integrin and an ADAM distintegrin domain, that inhibit endothelial cell migration, or that inhibit angiogenesis, comprising combining at test compound with an integrin or with endothelial cells and with an ADAM distintegrin domain polypeptide that binds to the integrin or endothelial cells and determining whether the test compound delsers the birding of the ADAM distintegrin domain polypeptide to the integrin or endothelial cells.

[0018] These and other aspects of the present invention will become evident upon reference to the following detailed description, examples, and claims.

DETAILED DESCRIPTION OF THE INVENTION

A. Abbreviations and Terminology Used in the Specification

16 [0019] "4-189" and "4-188 ligand" (4-188-L) are polypeptides described, inter alia, in U.S. Patent No. 5,674,704, including soluble forms thereof.

[0020] "ADAMs" are a family of transmembrane glycoproteins having disintegrin and metalloproteinase domains, also called MDC, metalloprotease/disintegrin/cysteine-rich proteins.

[0021] "Dis" is a disintegrin domain; "ADAMdis" is an ADAM disintegrin domain.

[0022] *CD40 ligand" (CD40L) is a polypeptide described, inter alia, in U.S. Patent No. 5,716,805, including soluble forms thereof.

[0023] "CD148" is a protein tyrosine phosphatase, also called DEP-1, ECRTP, and PTPRJ. CD 148 binding proteins are described in Daniel et al., PCT Publication No. WO 00/15258, 23 March 2000.

[0024] "DMEM" is Dulbecco's Modified Eagle Medium,

5 [0025] "FACS" is fluorescence activated cell sorting.

[0026] "Fit3t" is Fit3 ligand, a polypeptide described, inter alia, in U.S. Patent No. 5,554,612, including soluble forms thereof.

[0027] "HRMEC" are human renal microvascular endothelial cells.

[0028] "HMVEC-d" are human dermal microvascular endothelial cells.

[0029] "mAb" is a monoclonal antibody.

[0030] *MDC* is a family of cysteine-rich proteins having metallogroteass and disintegrin domains, also called ADAM, 100311 *Nectin 3* is a cell adhesion molecule in the nectin family (which is described, inter alia, in Satoh-Horikawa et

at. J. Biol. Chem. 275(14):10291, 2090). The GenBank accession numbers of human nectin-3 nucleic acid and polypeptide sequences are AF282874 and AAF97597 respectively (Reymond et al., 2000).

35 [0032] "PMA" is phorbol-12-myristate-13-apetate.

[0033] "Tek," which has also been called Tie2 and ork, is an receptor tyrosine kinase (RTK) that is predominantly expressed in vascular endothelium. The molecular diorsing of human Tek (ork) has been described by Ziegler, U.S. Patteri No. 5,447,860. "Tek antagonisis" are described, inter alia, in Cerretti et al., PCT Publication No. WO 00/75925, 14 December 2000.

40 [0034] "TNF" is tumor necrosis factor, "TNFR" is a tumor necrosis factor receptor, including soluble forms thereof, "TNFR/FC" is a tumor necrosis factor receptor-Fc fusion polypeptide.

[0035] "TPANL" is TNF-related apoptosis-inducing ligand, a type II transmembrane polypeptide in the TNF family described, inter alia, in U.S. Patent No. 5,763,223, including soluble forms thereof.

[0035] "TWEAK" is TNF-weak effector of apoptosis, a type if transmembrane polypeptide in the TNF Ismily described, inter alia, in Chicheportiche et al., J. Eiol. Chem., 272(51);32401, 1997, including soluble forms thereof. "TWEAK-R" is the "TWEAK receptor," which is described, inter alia, in U.S. Serial Numbers 60/172,2678 and 60/203,347 and Feng et al., Am. J. Pathol. 150(4):1253, 2000, including soluble forms thereof. TWEAK-RYFc is a TWEAK receptor-Fc fusion polypeotide.

[0037] "VEGF" is vascular endothelial growth factor, also known as VPF or vascular permeability factor.

B. ADAM Polypeptides and ADAM Disintegrin Domain Polypeptides

[0038] At least thirty ADAMs have been described. Table 1 provides reference information for selected human ADAMs. [0039] ADAM distringin domains show sequence homology to the snake venor dishtragrins, and are characterized by a transwork of orveitines. For example, a typical distribution sequence comprises a framework such as:

The sequences of several ADAM disintegrin domains are shown in Table 2 and in the Sequence Listing.

[0040] "The present invention encompasses the use of various forms of ADAM disintegrin domains that retain at least one activity selected from the group consisting of integrin binding activity, inhibition of endothelial cell riligration, and inhibition of englogenesis. The term "ADAM disintegrin domain, with or without other ADAM domains polypeptide" is intended to encompass polypeptides containing all or part of a native ADAM disintegrin domain, with or without other ADAM domains (such as the cysteine-tel region), as well as related forms including, but not finited to: (a) tragments, (b) variants, (c) detroited, (c) fixing polypeptides, and (e) multiment forms (multimens). The ability of these related forms to inhibit integrin binding, endothelial cell miligration, and/or inhibition of angiogenesis may be determined in vitro or in vivo by using methods such as those exemptilified before or by using other assaws (nown in the ext.

Table 1

			Table 1	
		Selecte	d Members of the ADAM Family	
15	ADAM	Other Names	GenBank Accession Number (Human)	Published Description
	ADAM-8	MS2, CD156	D26579	Genomics 41(1):56, 1997
	ADAM-9	MDC9, meltrin gamma	U41766	J. Cell. Biol. 132(4):717, 1996
ij.	ADAM-10	MADM, kuzbanian, reprolysin	AF009615	J. Biol. Chem. 272(39):24588, 1997
	ADAM-15	Metargidin, MDC15	U46005	J. Biol. Chem. 271(9):4593, 1996
	ADAM-17	TACE, cSVP	U86755	WO 96/41624
8	ADAM-20	SVPH1-26	AF029899	WO 99/23228
	ADAM-21	SVPH1-8	AF029900	WO 99/36549
	ADAM-22	SVPH3-13, MDC2	AB009671	WO 99/41368
	ADAM-23	SVPH3-17, MDC3	AB009672	WO 99/41388
2	ADAM-29	SVPH1	AF171929	Biochem, Biophys, Res. Commun, 263;810, 1999

[0041] The term "varient" includes polypeptides that are substantially homologous to native ADAM disintegrin domains, but which have an amino acid sequence different from that of a native ADAM disintegrin domain because of one or more deletions, insertions or substitutions. Particular embodimens include, but are not limited to, ADAM disintegrin domain polypeptides that comprise from one to ten deletions, insertions or substitutions of amino acid residues, when compared to a native ADAM disintegrin domain polypeptides are those variants of ADAM disintegrin domain polypeptides are those variants that are naturally occurring, such as allele forms and elternatively spliced forms, as well as variants that have been constructed by modifying the amino acid sequence of a ADAM disintegrin domain polypeptide or the nucleotide sequence of a nucleic acid encoding a ADAM distincerin domain polypeptide.

[0042] Generally, substitutions for one or more amino acids present in the native polypeptide should be made conservative). Exemples of conservative substitutions include substitution of amino acids outside of the active domaintly, and substitution of amino acids trated one taken the secondary endor tratifary structure of the ADAM disinleginf domain. Additional examples include substituting one alighantic residue for another, such as the, Val, Leu, or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Giu and Asp; or Gin and Asn, or substitutions of one aromatic residue for another, such as between Lys and Arg; Giu and Asp; or Gin and Asn, or substitutions of one aromatic residue for another, such as Phe, Trp, or Try for one another. Other such conservative substitutions, for example, substitutions of entire regions having similar hydrophobiolity characteristics, are known in the art

[043] In some preferred embodiments the ADAM disintegrin domain variant is at least about 70% Identical in amino acid sequence to the amino acid sequence of a native ADAM disintegrin domain; in some preferred embodiments the ADAM disintegrin domain variant is at least about 05% identical in amino acid sequence of a native ADAM disintegrin domain variant is at least about 05% identical in amino acid sequence of a native ADAM disintegrin domain variant is at insast about 05% identical in amino acid sequence to the amino acid sequence of the option acid sequence of the amino acid

about 99% identical in amino acid sequence to the arriino acid sequence of a native ADAM disintegrin domain.

[9044] Percent identity, in the case of both polypeptides and nucleic acids, may be determined by visual Inspection. Percent identity may be determined using the alignment method of Needleman and Wursch (J. Mol. Biol. 484-45, 1970) as revised by Smith and Waterman (Art. Appl. Mark 2-482, 1981. Preferably, percent identity is determined by using a computer program, for exemple, the GAP computer program version 10x available from the Genetic Computer Group (GCG; Madison, WI, see also Devereux et al., Nucl. Acids Res. 12:387, 1984). The preferred default parameters for the GAP program includes (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides, and the weighted comparison matrix (or floakeov and Burges, Nucl. Acids Res. 14-674, 9188, and escribed by Schwartz and Dayhoff, eds., Atlas of Protein Sequence and Structure, National Blomedical Research Foundation, pp. 563-368, 1979 for arrains acids; (7) a penalty of 30 (amino acids) or 50 (nucleotides) for each garps, and (4) no maximum penalty for long gaps. Other programs used by one skilled in the art of sequence comparison may also be used. For fragments of ADAM disintegrin domains, the percent identity is calculated based on that portion of ADAM disintegrin domain that is crossent in the framment.

(945) When a deletion or insertion strategy is adopted, the potential effect of the deletion or insertion on biological activity (such as integrin binding activity, inhibition of endothelial cell intigration, or inhibition of angiogenesis) must be considered. Schurits of the hiventhie polyperidises may be constructed by deleting terminal or internal residuous or sequences. Additional guidance as to the types of mutations that can be made is provided by a comparison of the sequence of ADAM disintagrin domain polyperidises that have similar structures, as well as by performing structure area less than the market polyperidises.

structural analysis of the inventive polypeptides.

[0048] The term "varian" islas includes ADAM disinlegrin domain polypeptides that are encoded by nucleic acids capeble of hybridizing under moderately stringent conditions (e.g., prevessing solution of \$ X SSC, 0.8% SDS, 1.0 mM EDTA (pH 8.0) and hybridizing moderately stringent conditions to EON-as equences encoding ADAM disintegrin domain polypeptides, and which encode polypeptides that retain at least one activity selected from the group consisting of integrin binding activity, inhibition of encodinelial cell migration, and inhibition of angiogenesis. The skilled artistance and eleterine seditional combinations of salt and temperative that constitute moderate hybridization stringency. Conditions of higher stringency include higher temperatures for hybridization and post-hybridization washes, and/or lower salt concentration.

[0047] Mutations can be introduced into nucleic acids by synthesizing oligonucleotides containing a mutant sequence, fainted by restriction sites exhibiting liquid in regiments of the nealive sequence. Following ligidation, the resulting necessary objects of the result of sequence encodes a variant having the desired amino acid insertion, substitution, or delation. Alternatively, oligonucleotide-directed site-specific mutagenesis procedures can be employed to provide an altered spone having parcular codors altered according to the substitution, delation, or insertion required. The well known polymenses chain section (PCR) procedure sites may be employed to generate and amplify a DNA sequence encoding a desired polypeptid of or fragment hereof. Cligonucleotides that define the desired termind of the DNA regiment are employed as 5° and of primes. The oligonucleotides may additionally contain recognition sites for restriction endonucleases to facilitate insertion of the amplified DNA fragment are entitled to the second of the amplified DNA fragment are entitled to the second of the amplified DNA fragment are entitled to the second of the amplified DNA fragment are entitled to the second of the amplified DNA fragment are entitled to the second of the amplified DNA fragment are second or the amplified DNA fragment are second or the second o

[0048] The present invention further encompasses the use of ADAM disintegrin domain polyopetides with or without associated nutive-patient glycosylation. ADAM disintegrin domain expressed in yeast or mammalian expression systems (e.g., c05-) or c05-) celso may be similar to or significantly different from a native ADAM disintegrin domain polyopetide in molecular weight and glycosylation pattern, depending upon the choice of expression systems. Expression of ADAM disintegrin domain polyopetide in bacterial expression systems, such as E. co.ly provides non-glycosylated molecular. Different note cells may also process polypeptides differentially, resulting in heterogeneous mixtures of polypeptides with variable N- or C-termital.

(5049) The primary amino acid structure of ADAM disintegrin domain polypeptides may be modified to create derivatives by forming covalent or aggregative conjugates with other chemical moleties, such as glosoyl groups, lipids, phosphate, acetly groups and the like. Covalent derivatives of ADAM disintegrin domain polypeptides may be prepared by liming particular functional groups to ADAM disintegrin domain amino acid side chains or at the N-terminus or C-terminus of a ADAM disintedni domain polypertide.

[0050] Fusion polypeptides of ADAM dishrtegrit domains that are useful in practicing the invention include covelent or aggregative conjugates of ADAM dishrtegrit of contains with other polypeptides, such as by synthesis in recombinant cuture as N-terminat or C-terminal fusions. One class of huston polypeptides are discussed below in connection with ADAM dishrtegrin ofspomers. As another example, a fusion polypeptide may comprise a signal peptide (winch is associated as the content of the content of the N-terminal region of the ADAM dishrtegrin of th

the ceil

[0051] Secreted soluble polypeptides may be identified (and distinguished from its non-soluble membrane-bound counterparts) by sepretrating institut calls which express the desired polypeptide from the culture medium, ag, by centrifugation, and assaying the medium (supernatant) for the presence of the desired polypeptide. The presence of the desired polypeptide. The presence of the desired polypeptide in the medium indicetes that the polypeptide was secreted from the cells and thus is a soluble form of the polypeptide. Subtle polypeptides may be prepared by any of a number of conventional techniques. A DNA sequence anoding a desired soluble polypeptide soluble polypeptide soluble polypeptide. Such as polypeptide soluble polypeptides of the desired polypeptide soluble polypeptides of the desired polypeptide. Soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide. Soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide. Soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide soluble polypeptide soluble soluble polypeptide soluble solub

19082] Solubio ADAM dishtegrin domain polypeptides comprise all or part of the ADAM dishtegrin domain, with or without additional segments from the extracellular portion of the ADAM (such as the cystaine-rich region) but generally lack a transmerminare domain that would cause retention of the polypeptide at the cell surface. Soluble polypeptides may include part of the transmembrane domain or all or part of the cytoplasmic domain as long as the polypeptide is secreted from the cell in which it is produced. Examples of soluble ADAM dishirtegrin domain polypeptides are provided in the examples. In some preferred embodiments of the present invention, are multiment form of a soluble ADAM dishirtegrin domain polypeptide is used to inhibit integrin binding to ligands and, hence, integrin biological activity. In some most preferred embodiments the soluble ADAM dishirtegrin domain polypeptide is used to inhibit embodibation and/or inhibit angiogenesis. These inhibitory activities may include both integrin-mediated and integrin-independent mechanisms.

[0053]. ADAM distinsign domain multimers are covalently-inited or non-covalently-inited multimers, including dimers, triners, and injent multimers. (Dignomers may be inked by distulbed bonds formed between cysteline residues on different ADAM distinsign domain polypeptides. One embodiment of the invention is directed to multimers comprising multiple ADAM distinsign domain polypeptides. Such peptides multi be period in terractions between peptide midelete fused to the ADAM distinsign domain polypeptides. Such peptides multiple by a peptide infects (splacers), or peptides that have the property of promoting multimerization. Leucine Zippers and certain polypeptides detaived from antibodies are among the peptides what can promote multimerization of ADAM distinsign domain polypeptides attached thereon, as described in more detail below. In particular embodiments, the multimers comprise from two to four ADAM distinting holypendiles.

[0054] In some ambodiments, a ADAM distinisgrin domain multimer is prepared using polypeptides derived from immunoglobulins, Preparation of fusion proteins comprising certain heterologicus polypeptides lused to various portions of antibody-derived polypeptides (including this Fo domait) has been described, e.g., by Astrikanazi et al. (Proc. Natl. Acad. Sci. USA 88:1055, 1991); Byrn et al. (Nature 344-677, 1990); and Hollenbaugh and Arutfo ("Construction of immunoglobulin Fusion Proteins", in Current Proteosis in Immunoglobulgy, Suppl. 4, pages 10.13.11.01.31, 1,1992).

[0055] A preferred embodiment of the present invention is directed to an ADAM disintegrin domain (ADAMdis) direct comprising you vision polypeoptides created by Issing an ADAM disintegrin domain to an Fig onlypeoptide. A gane fusion encoding the ADAMdis-Fo fusion polypeoptide is inserted into an appropriate expression vector. ADAMdis-Fo fusion polypeoptide are expressed in host cells transferred with the recombinant expression vector. And allowed to assemble much like antibody molecules, whereupon interchain disalfide bonds from between the Fo moleties to yield violated soluble ADAMdis-Fo polypeoptides. The term Fo polypeoptide and rained herein includes anxiety and with one of polypeoptides derived from the Foreign of an antibody. Truncated forms of such polypeoptides containing the hinge region that promotes directions are also included.

[0.65g] One suitable Fc polypeptide, described in PCT application WO 93/10151, is a single chain polypeptide extending from the N-terminal ships region to the native C-terminus of the Fo-region of a human [g.51 antibody, Another useful Fc polypeptide is the Formatine described in U.S. Pittert 5,457,005 and by Baum et al., EMBOL 3, 133992; 1984. The amino acid sequence of this muticin is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ma, amino acid 20 has been changed from the union of the control of the native formation of the control of

© [0057] In other embodiments, a soluble ADAM disintegrin domain polypeptide may be substituted for the variable portion of an antibody heavy or light chains, if fusion proteins are made with both heavy and light chains of an antibody, it is possible to form an ADAM disintegrin domain multimer with as many as four soluble ADAM disintegrin domain polypeptides.

[0058] Alternatively, the ADAM distriction domain multimor is a fusion polypectide comprising multiple. ADAM distritegrint domain polypectides, with or without peptide linkers (spacers), or peptides that have the property of promoting multimorization. Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,455,233. A DIAM sequence encoding a desired peptide linker may be inserted between, and in the same reeding frame es, the DIAM sequences encoding ADAMS, using conventional techniques known in the art. For example, a chemically synthesized.

oligonusiaeotiste encoding the linker may be ligited between sequences encoding ADAMulis. In particular embodiments, a tusion protein comprises from two to lour ADAM disintegrin domain polypeptides, separated by peptide linkers, a tusion protein comprises from two to lour ADAM disintegrin domain multimets involves use of a leucinia zipper domain Leucine zipper domains ere peptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in averated INA-binding proteins (Landenbulz et al., 2-dence 24ch1756), 1988, and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivativas thereof that dimerize or frametra. Exempts of seusche zipper domains suitable for graduling soluble oligometric proteins are discribed in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein (ISPD) described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein (ISPD) described in Pctper that allows for stable timeration of a heterologius protein lipses there is described in Parsilow et al., Serini. Immunol. 6257, 1994. Recombinant fusion polypeptides are expressed in situation hast cells are polyper people are expressed in situation between the ADAM disintegrin domain polypeptide leused to a leucine zipper reported are expressed in situation between the ADAM disintegrin domain multimer that forms is recovered from

C. Recombinant Production of ADAM Disintegrin Domain Polypeptides

[0060] The ADAM disintegrin domain polypeptides used in the present invention may be prepared using a recombinent expression system. Host cells transformed with a recombinant expression vector encoding the ADAM disintegrin domain polypeptide are outlaned under conditions that promote expression of ADAM disintegrin domain and the ADAM disintegrin domain provided are could disintegrin domain and the ADAM disintegrin domain and the ADAM disintegrin domain are covered. ADAM disintegrin domain polypeptides can also be produced in transgenic plants or animals.

[0051] Any suitable excression system may be employed. Recombinant expression vectors include DNA encoding an ADAM disintegring domain polypeptide operably histed is autibable transcriptional and translational regulatory nucleotide sequences, such as those darkerform a mammalian, microbial, viral, or insect gene. Nucleotide sequences are operably linked when the regulatory sequence functionally relates to the ADAM distintegrin domain DNA sequence list operably Enked to an ADAM distintegrin domain DNA sequence list promoter nucleotide sequence controls the transcription of the ADAM distintegrin domain DNA sequence list promoter nucleotide sequence controls the transcription of the ADAM distintegrin domain DNA sequence list promoter nucleotide sequence control transcription and translation initiation and termination. A sequence encoding an appropriate sequences which control transcription and translation initiation and termination. A sequence according an appropriate signal peptide (searcher) leader) may be fueed in frame to the ADAM disintegrin domain sequence so teather ADAM disintegrin domain polypeptide is initially translated as a fusion protein comprising the signal peptide. A signal peptide that is functioned in the literated host cells promotes extracelular secretion of the ADAM disintegrin domain polypeptide. The signal peptide is cleaved from the ADAM distintegrin domain polypeptide in the literated host cells promotes extracelular secretion of the ADAM disintegrin domain polypeptide. The signal peptide is cleaved from the ADAM distintegrin domain polypeptide special period is cleaved from the ADAM distintegrin domain polypeptide is continued and extracelular period is cleaved from the ADAM distintegrin domain polypeptide special period is continued and extracelular period period special period sp

[0682] Using the tenhiques of recombinant DNA including mutagenesis and the polymerase chain reaction (PCR), the skilled eritan can produce DNA sequences bat encode ADNA distingth domain polypedifies comprising various additions or substitutions of amino add residuae or sequences, or deletions of terminal or internal residuaes or sequences, including ADNA distingtion domain in fragments, variants, derivatives, multilares, and layton polypedifies.

[0063] The procedures for purifying expressed ADAM disintegrin domain potypeptides will vary according to the host asystem employed, and whether on orthe recombinant potypeptides is searested. ADAM disintegrin domain potypeptides may be putified using methods known in the art, including one or more concentration, satisfing-out, ion exchange, hydro-phabic internation, affiling purification, HPLC, or stee exclusion between acting responsible, put one or more concentration affinity purification. HPLC, or stee exclusion between acting principations, Fusion potyperciples compressing or for more different principal continuous.

D. Therapeutic Methods

hosts are known in the an.

the culture supernatant.

7 [0064] The disclosed methods may be used to inhibit integrin binding and integrin biological activity, and to inhibit endothelial cell intigration, and/or angiogenesis in a mammal in need of such treatment. The treatment is advantageously administrated in order to prevent the onset or the recurrence of a disease or condition mediated by an integrin, or to treat a mammat that has a disease or condition mediated by an integrin.

[0055] Examples of the therapeutic uses of ADAM dishragin domain polyceptides and compositions thereof include the treatment of individuals afflicted with conditions mediated by angiogenesis such as coular disorders, demetological disorders, and malignant or midatatic conditions, inflammatory diseases, osteoporosis and other conditions mediated by accelerated bone resorption, restencists, inappropriate platelet activation, recruitment, or aggregation, thrombosis, or a condition resulting issues repair or wound healing.

[0066] Among the ocular disorders that can be treated according to the present invention are eye diseases characterized by ocular neversecularion including, but not limited to, disheber tetnopethy of major complication of disberted, retinopathy of prematurity (this devastating eye condition, that frequently leads to chronic vision problems and carries a high risk of bilindness, is a severe complication during the care of premature infants), neovescular glaucoma, retinoblations, retrotrectly fibrighesia, tudeosis, welfels, medical degeneration, and comes girat neovesculerization. Other sys inflammatory diseases, ocular tumors, and diseases associated with chronical or risk neovescularization can also be treated according to the present invention.

[0067] The present invention can also be used to treat malignant and metastatic conditions such as solid tumors. Solid tumors include both primary and metastatic sercemas and carolinomas.

[0068] The present invention can also be used to treat inflammatory diseases including, but not fimited to, arthrifs, rheumatism inflammatory bowel disease, and osoriasis.

[0069] Among the conditions mediated by inappropriate platelet activation, recruitment, aggregation, or thrombosis that can be treated according to the present invention are coronary artery disease or injury, myocardial infarction or injury following myocardial intention, stroke, unstable angina, atherosclerosis, arteriosclerosis, preeclampsia, embolism, platelet-associated ischemic disorders including lung ischemia, coronary ischemia, and cerebral ischemia, restenosis following percutaneous coronary intervention including angioptasty, atherectomy, stent placement, and bypass surgery, thrombotic disorders including coronary artery thrombosis, persphal artery thrombosis, intracardiac thrombosis, perspheral artery thrombosis, venous thrombosis, thrombosis and coagulopathies associated with exposure to a foreign or injured tissue surface, and reocclusion following thrombosis, deep venous thrombosis (DVT), pulmonary embolism (PE), transient jachemic attacks (TiAs), and another conditions where vascular occlusion is a common underlying feature. In some embodiments the methods according to the invention are used in individuals at high risk for thrombus formation or reformation, advanced coronary aftery disease, or for occlusion, reocclusion, stenosis and/or restenosis of blood vessels, or stroke. In some embodiments the methods according to the invention are used in combination with angioplasty procedures, such as balloon andioplasty, laser andioplasty, coronary atherectority or similar techniques, carotid endarterectorily, anastomosis of vascular grafts, surgery having a high risk of thrombus formation (i.e., coronary bypass surpery, insertion of a prosthetic valve or vessel and the like), etherectomy, stent placement, placement of a chronic cardiovascular device such as an in-dwelling catheter or prosthetic valve or vessel, organ transplantation, or bypass

[0070] Other diseases and conditions that can be treated according to the present invention include benign tumors of and prenoplestic conditions, mycoardial angiogenesis, hamoprillic joints, soleroderms, vascular adhesions, astimns and allergy, eczeme and dermatitis, graft versus host disease, sopsis, edult respirator distress syndrome, telangiectastis, and wound granulation.

[0071] The methods according to the present invention can be tested in in vivo animal models for the desired prophylication of thereguide activity, as well as to determine the optimal therepeated designe, prior to administration to humans. [0072] The amount of a particular ADAM disintegrin domain polypeptide that will be effective in a particular method of treatment depends upon page, type and severity of the condition to be treated, body weight, desired duration of treatment, method of administration, and other parameters. Effective desages are determined by a physician or other qualified method: professional Typical effective desages are about 0.0 mg/kg to about 10.0 mg/kg to obsult 100 mg/kg body weight. In some preferred embodiments the desage is about 0.1-80 mg/kg in some preferred embodiments the desage is about 0.5-10 mg/kg. The dosage for local administration is pixelled juvent han for systemic administration, in some embodiments a single administration is sufficient; in some embodiments the ADAM disintegrin domain is administered as multiple dosas aver one or more abovs.

[0073] The ADAM dishrtegrin domain polypeptides are typically administered in the form of a phermacoudical composition comprising one or more pharmacoudically acceptable carriers. Phermacoudically acceptable carriers included dilute onts, fillers, adjuvants, exciptients, and vehicles which are pharmaceutically acceptable for the route of administration, and may be aqueous or elegificious auspensions formulated using suitable dispersing, wetning, and suspending agents. (D074] Pharmaceutically acceptable certifier are generally steller and free of properlic agents, and may include water, oils, solvens, salts, sugars and other carbohydrates, emulsifying agents, buffering agents, arthrintrobial agents, and celetating agents. The particular pharmaceutically acceptable carrier and the ratio of active compound to currier are determined by the solubility and chemical properties of the composition, the mode of administration, and standard pharmaceutical practice.

[D075] The ADAM distrilegrin domain polypeptides are administered to the patient in a manner appropriate to the indication. Thus, for example, ADAM distrilegrin domain ophypeptides, or pharmaceutical compositions thereof, may be administrated by intravenous, transformal, intradermal, intransect, eligible, or a transect, eligible, intransect, eligible, intransect, eligible, or a transect, eligible, eligi

[0076] In certain embodiments of the claimed invention, the treatment further comprises treating the mammal with one or more additional the apoutic agents. The additional the appendix agents in any be administered prior to, concurrently

with, or following the administration of the ADAM dishtagrin domain polypeptide. The use of more than one therapeutic agent is particularly advantageous when the mammal that is being treated has a solid tumor. In some embodiments of the claimed invention, the treatment further comprises treating the mammal with radiation. Radiator, including brachytherapy and seitherapy, may be administered prior to, concurrently with, or following the administration of the ADAM dishiptedin demain polypeotific and/or additional therapeutic apending.

[0077] In some preferred embodiments the method includes the administration of, in addition to an ADAM disintegrin domain polypspide, one or more therapeurics selected from the group consisting of allysting spenis, antimateboties, vince askaloide and other plant-derwed chemotherapeurics, antitumor artibiotics, antitumor enzymest, topolsomarses inhibitors, piletnum analogs, adrenocortical suppressants, hormones and antihormones, artibodies, immunotherapeurics, radichareactics, antitumoical resources modifiers.

10078] In some preferred embodiments the method includes administration of, in addition to an ADAM distritogrin tomain polypeptide, one or more interpeutics selected from the group consisting of cisptalin, cyclophosphamide, mechloraturine, meliphasin, bleomycin, carboptalin, fluorouracil, 5-fluorodeoxyuridine, methotraxette, taxul, separaginase, vincaristino, and viribitastine, lymphokines and cytokines such as interfecultins, interferors (alpha, bets. or delate, and TNF, chlorarbucil, busuffer, camustine, formatine, semustine, attendaction, dacerbazine, cytotactine, mercepopolinis, titi oquanine, vindesine, etoposide, teniposide, deciliomycin, daunorubicin, doxorubicin, pleamycin, pleamycin, milomycin, Lesparaginases, hydroxyurse, methylytydazine, militatue, tenxolien, fluoxymsferome, i.e. in hibitors, angiostatin, eriodistatin, kringle 5, angiopoletin-2 or other antagoniets of basic fibroblest or over flactor, and COXS-2 inhibitors.

[0079] In some preferred embodiments the method includes administration of, in addition to an ADAM distintegrin domain polypectifie, one or more therapeutic polypeptifies, including soluble forms thereof, selected from the propose sciented from the propose sciented from the propose content of the propose of the propo

2000) binding proteins, and needin-3 entlagonists.

[0080] In some preferred embodiments the ADAM disintegrin domain polypeptides of the Invention are used as a component of, or in combination with. "metronomic therspy," such as that described by Browder et al. and Klement et

al. (Cancer Research 60:1878, 2000); J. Clin. Invest. 1056); R15, 2000; see also Barrinaga, Science 288:245, 2000). [0081] As used hareful, the terms "haregur," therapeutic, "freed, and "freatment" generally include prophylaxis, it, prevention, in addition to therapy or treatment for an extant disease or condition. The methods of the present invention may be used as a first fine treatment, for the treatment of residual disease following primary therapy, or as an adjunt to other the rapies. Methods of measuring biological effectiveness are known in the art and are illustrated in the Examples below.

EXAMPLES

28

15

[0092] The following examples are intended to illustrate particular embodiments and not to limit the scope of the invention.

EXAMPLE 1

ADAM Disintegrin Domain Polypeptides

[0083] This example describes one method for the recombinant production of ADAM distintegrin domain polypeptides. [0084] Expression cassettee encoding an Igidappa leader asquence, ADAM distintegrin domain, and Charminal Foreign were constructed in bacterial plasmids than transferred into eukaryotic expression vectors (DDC408, EMBO J. 10:2821, 1991, or another marmatian expression vector). The coding regions of the various constructs are summarized in Table 2. In addition to the distinction domain, these constructs are code additional portions of the extracellular portion

of the ADAM (e.g., cysteine-rich region and EGF-fike domain).

[0085] The expression vectors were transfeded into COS-1, CV-1/EBNA, or 283/EBNA cells. Two days after transfection the cells were ⁵⁰S labeled for four hours. Supernalaris and total cell lystes were prepared and aliquots were immunoprecipitated using protein A-septranse basets to capture the Fc tagged potypaptices. ⁵⁰S labeled ADAM distributions of the cells are the

legrin-Fc polypeptides were run on 8-19% reducing gels and detected via autoratiography.

[D086] The cell type that produced the most soluble protein in the supernatiant was used in a large scale (T-175 format, 20 flexks) transient transfection, and approximately one fiter of supernatiant was harvested after one week. ADAM distinctions for the producing transfer transfection, and approximately one fiter of supernation was incompanily protein A column). The

polypepitides were characterized by determining the N-terminal amine acid sequence, smino acid composition, and protein integrity (SDS-PAGE under reducing and non-reducing conditions) before the polypeptides were used in FACS, immunoprecipitations, and biological assays such as those desortibed below.

Table 2

		4.1	ADAM disintegrin ^{1,3} (dis	T
Construct	SEQ ID NOs: DNA/polypeptide	IgK Leader ^{1,2}	Framework)1.4	Fc Region
ADAM-8dis-Fc	1/2	1-20	23-264 (34-91)	267-494
ADAM-9dis-Fc	3/4	1-20	23-303 (34-92)	306-633
ADAM-10dis-Fc	5/8	1-20	23-235 (34-99)	238-465
ADAM-15dis-Fc	7/8	1-20	23-292 (34-92)	295-522
ADAM-17dis-Fc	9/10	1-20	23-216 (34-93)	219-446
ADAM-20dis-Fc	11/12	1-20	23-305 (34-91)	308-535
ADAM-21dis-Fc	13/14	1-20	23-293 (34-91)	296-523
ADAM-22dis-Fc	15/16	1-20	23-312 (34-92)	315-542
ADAM-23dis-Fc	17/18	1-20	23-310 (34-91)	313-540
ADAM-29dis-Fc	21/22	1-20	23-298 (34-91)	301-528

1 residues in the polypeptide sequence

2 the predicted cleavage site is after residue 20

3 segment of the construct that includes ADAMdis, but may also contain additional ADAM sequences

4 disintegrin framework, e.g., SEQ ID NO:20

30 EXAMPLE 2

15

20

Binding of ADAM Disintegrin Domain Polypeptides to Cells

A. Binding to Endothelial cells

[0087] This example describes a flow cytometric integrin m/Ab based binding inhibition assay, which is used to show binding of ADAM dishitegrin-Popolypeptides to Integrins expressed on the surface of endothelial cells. Human endothelial cells express e.g., v, Qs, Pg, Ag, -v, Qs, -qs, -qs, and -qs, integrins.

[0088] Primary human dermal microvascular endothelial cells (HMVEC-d) were maintained in supplemented endotheilal growth medium (Clonetics Corporation, Walkersville, MD). The ADAM disintegrin-Fc polypeptides produced in Example 1 were shown to bind specifically to HMVEC-d. Monoclonal antibodies specific for human integrins u. B. (LM609, anti CD51/61, Chemicon, Temecuia, CA Brooks et al., Science 264:569, 1994), coll. (BHA2.1 enti CD49b, Chemicon, Wang et al., Mol. Blol. of the Cell 9:865, 1998), a.S. (SAM-1 anti CD49e, Biodesign, A. te Velde et al., J. immunol, 140: 1548, 1988), α₆8, (ASC-6 anti-CD49c, Chemicon, Pattaramata) et al., Exb. Cell. Res. 222; 281, 1996), α₆8, (HP2/1 anti-CD49d, Immunotech, Marseilles, France, Workshop of the 4th International Conference on Human Leukpoyte Differentistion Antigens, Vienna Austria, 1989, workshop number p091), q₆8_c. (GoH3 anti CD49f, immunorech, Workshop 4th International Conference on Human Leukocyte Differentiation Antigens, workshop number p055), $\alpha_{\rm e}\beta_{\rm e}$ (439-98 anti-CD104, Pharmingen, San Diego, CA., Schlossman et al., 1995 Leukocyte Typing V: White Cell Differnitation Antigens. Oxford University Press, New York), and o. 8x (MAB 1961, Chemican International, monoclonel anti-human Integring, 8x mAb, IgG1 isotype, inhibits a.B., mediated binding/adhesion to vitronectin/libronectin; Weinaker, et al., J. Biol. Chem, 269:6940, 1994) were also shown to bind specifically to HMVEC-d. Each of these antibodies is known to specifically block blinding of the indicated integrin to its ligands (e.g., fibronectin, vitronectin, fibrinogen). The ability of integrin mAbs to inhibit the binding of ADAM disintegrin-Fc polypeptides reveals which integrins the disintegrin domains bind and, indirectly, which integrin binding activities the disintegrin gomeins are able to antagonize. The ability of the antibodies to inhibit binding of the ADAM disintegrin-Fc polypeptides to andothelial cells was tested as described below.

[0099] Prior to performing binding studies, HMVEC-d were removed from culture vessels using trypsin-EDTA. The cells were washed in media portaining serum and resuspended in binding medium which consisted of PBS containing

1 mM Ca2+, 1 mM Mg2+ and 0.5 mM Mn2+, 0.1% sodium azide, 10% Normal goat serum, 2% rebbit serum and 2% fetal bovine serum. Under these binding conditions, ADAM-6, -9, -10, -15, -17, -20, -21, -22, -23, and -29dls-Fe all bind to human endothelial cells.

[0090] One hundred microfiters of cell suspension, containing 200,000 to 800,000 HMVECd, were added to 12/75mm plastic test tubes. Monocheral antibodies specific for one of the integrine, or a control monoclorist antibody (CD22 or M15), were added to the cell suspensions at a concentration of 100 µg/ml (54 fold mass excess) 15 minutes prior to addition of disintegrin-Fo-tusion proteins. ADAM distintegrin-Fo-ploppeptides and control Fo-tusion polypeptides (P7/SILF) were added, at various concentrations from 12.5 to 20 µg/ml, to the cell suspensions and incubated for 1 hour at 30° C. Unbound Fo-polypeptides were washed away by certifugation of cells in 2 mis of binding media. The varieties described the proteins were resupended in binding mediam and than incubated at 30° C for 30 minutes. After centrifugation and washing of the cell pellets, the cells were resuspended in binding mediam and bound arth-human Fo-bid was detected by adding steptical viden-phytocerythrin conjugate to the cell suspension at a 1:1000 dilution (1 µg/ml) and incubating it 30° C for 30 minutes. The unbound distribution in the properties of the cells were resuspended in binding mediam and bound arth-human Fo-bid was detected by adding steptical viden-phytocerythrin conjugate to the cell suspension at a 1:1000 dilution (1 µg/ml) and incubating it 30° C for 30 minutes.

propioum locide. The level of fluorescent binding (disintegrin-Fc binding) was determined by flow cyrometry, [0091]. The level of binding of each ADAM disintegrin-Fc polypeptide was determined in the presence of anti-integrin specific mAb and in the presence of control mAb. Both the intensity of binding (MFI) and the percentage of cells binding were determined. Percent inhibition was calculated using the formula [1 - (MFI control-MFI integrin mAb) / MFI control. The results of these studies are summarized in Table 3.

(0082] ADAM-15, 1-17, -20 and -22 disintagin domain polypeptides bound to α,β_c, ADAM 23 disintagrin domain polypeptide bound to α_cβ_c, ADAM-15, -17, -22 and -23 disintagrin domain polypeptides bound to α_cβ_c, ADAM-10, -17, -22 and -23 disintagrin domain polypeptides bound to α_cβ_c, and excess of a non blocking α,β_c arithody did significantly affect the birding of ADAM-10, -22, and -23 disintegrin polypeptides to endothelial cells, suggesting that these ADAMdso polypeptides interact with integrin sizes other than or in addition to the ligand (e.g., libronactin, vitronactin) binding site. Based upon results from a different type of assay, Call et al. have reported that the ADAM-23 disintegrin domain interacts with the α,β_c integrin through an RiGD independent mechanism (Molec. Biol. of the Cell 11:1457, 2008).

[0093] Elinding experiments are repeated using other ADAM disintegrin domains and other monoclonal antibodies. ADAM disintegrin-Fo polypeptides that bind to selected integrins are further tested for the ability to disruption legin-ligand interactions and to modulate endothelial cell function, analogenesis, and other biolocical early distributions in vivo.

Toble 3

	Integrin Binding1 (+ ar - or ND, not done) and Percent (%) Binding2										
ADAM	$\alpha_{\nu}\beta_{3}$	612B1	α ₃ β ₁	$\epsilon r_4 \beta_1$	$\alpha_{5}\beta_{1}$	$\alpha_6 \beta_1.\alpha_6 \beta_4$	$\alpha_{\nu}\beta_{5}$				
ADAM-8	ND	ND	- (<10)	· (<10)	NO	ND	- <20)				
ADAM-9	- (<10)	· (<10)	- (<10)	· (<20)	-(<10)	- (<10)	· (<10				
ADAM-10	- (<10)	- (<10)	- (<10)	- (<20)	- (<10)	+ (48)	+ (25)				
ADAM-15	+ (60)	~ (<10)	~ (<10)	- (<20)	+ (30)	~ (<:10)	+ (25)				
ADAM-17	+ (50)	~ (<10)	~(<10)	- (c10)	-(<10)	+ (69)	· (<10				
ADAM-20	+ (58)	- (<10)	- (<10)	- (<10)	- (<20)	- (<10)	- {<10				
ADAM-21	~ (<10)	· (<10)	- (<10)	· (<10)	+ (54)	· (<10)	٠ (<10				
ADAM-22	+ (42)	· (<10)	- (<10)	· (<10)	+ (36)	+ (32)	· (<10				
ADAM-23	- (<10)	+ (22)	- (<10)	- (<10)	+ (49)	+ (31)	- (<10				

positive approx. 2X over background */percent linitiation of binding by ADAM-dis-Fc in the presence of 5-8 fold excess integrin mAb as compared to centrol mAb

36

40

50

B. Binding to Primary Human T-Cells

(9094) Primary human T-cells were purified from whole blood. These cells were used in FACS experiments to assess call surface binding of purified ADAMds-Fe polyapptiaes. ADAMds-Fe binding was sessessed with and without Con A (5 μg/ml) or immobilized OTK3 antibody (1 mg/ml, immobilized for 1 hour, 37°C) attribution. ADAMds-Fe polyapptiaes (20 μg/ml) were bound at either 4°C or 30°C in the presence of address (24+4, Mg++, Mn++, 6.5 mM each). Cell surface integim expression was assessed using a panel of mutine and rail artif-turnan integrin artibudies. ε₁, θ₁, μ₁, μ₂, μ₃, μ₄, μ₅, μ₆, μ₆

C. Sinding to Resting Platelets

filos [0095] Binding of ADAMdis-Fc polypeptides to citrated washed resting platelets was performed at 4°C or 90°C. Binding was analyzed by flow cytometry using a biotinylated-anti-human Fc specific antibody and streptavidin-PE. Resting platelets express the integrins CD4*CDD1 and CD48c. ADAM-9ds-Fc and ADAM-9ds-Fc bound resting platelets at 30°C was not inhibited by a ten-fold excass of CD4 to mAb.

EXAMPLE 3

200

622

Activity of ADAM Disintegrin Domain Polypeptides in a Wound Closure Assay

50069] A planar endothelial cell migration (wound closure) assey was used to quantitate the inhibition of angiogenesis by ADAM dishinating-free polepetities in vitro. In this assey, endothelial cell migration is measures as the rate of closure of a circular wound in a cultured cell monoleyer. The rate of wound closure is linear, and is dynamically regulated by agents that stimulate and inhibit appolageness in vivo.

[0097] Primary human renal microvascular endothelal calls, HRMEC, were lacitated, outtured, and used at the third passage after thawing, as described in Martin et al., In Vito Cell Dav Biol 325ch, 1997. Replicate circular tellations, "wounds," (800-800 micron disense) were generated in confluent HRMEC monolayers using a sticon-lipped drill press. At the time of wounding the medium (DMEM + 1% SSA) was supplemented with 20 might PMA (phorbol-12-my/slate-13-acetate), a range of concentrations of ADAM dishtreginf-to-polypepdise, contributions of PMA and ADAM dishtreginf-to-polypepdise, contributions of PMA and ADAM dishtreginf-to-polypepdise, and some analysis of the properties of shown in Table 5 shown i

[0038] The effect of ADAM-dis-Fc polypeptides on EGF-induced migration was also determined. For these experiments EGF [epidermal growth factor, 40 ng/ml] was added to the medium, instead of PMA, at the time of wounding. The results are shown in Table 5.

Table 4

			As	say			
Expt. ID	No Addition	PMA 20 ng/ml	PMA + igG	PMA + ADAM- 15dis-Fc	PMA + ADAM- 17dis-Fc	PMA + ADAM- 20dis-Fc	PMA + ADAM- 23dis-Fo
HL-H-142 15 μg/ml dis-Fc	0.9436 ¹ (0.0016) ²	0.0655 (0.00G4)		***************************************		0.0499 (0.0009) 72% ³	
HL-H-147 15 μg/mi dis-Fc	0.0244 (0.0023)	0.0424 (0.0002)	0.0449 (0.0012) 0%	0.0357 (0.0007) 37%			0.0225 (0.0022)

13

(continued)

			As	say			
Expt. ID	No Addition	PMA 20 ng/mi	PMA + IgG	PMA+ ADAM- 15dis-Fc	PMA + ADAM- 17dis-Fc	PMA + ADAM- 20dis-Fc	PMA + ADAM- 23dis-Fo
HL-H-153 15 µg/ml dis-Fc	0.0253 0.00013	0.0460 (0.0022)	0.0491 (0.006) 0%		0.0392 (0.0016) 33%	0.0388 (0.005) 36%	0.0317 (0.005) 703
HL-H-154 15 µg/ml dis-Fc	0.0119 (0.0012)	0.0312 (0.0016)			0.0283 (0.0008) 15%	0.0160 (0.0017) 79%	

1 Slopes to average triplicate Y values and treat as a single data point in order to test whether the slopes are significantly different

Table 5

Effect of ADAM	A-17, -20, and -23	Bals-Fc Polypepti	desin EGF-Induc	ed Endothelial Ce	ll Wound Closure	Migration Assay
Expt. ID	No Addition	EGF 40 ng/ml	EGF + IgG	EGF + ADAM- 17dis-Fc	EGF+ADAM- 20dis-Fc	EGF + ADAM- 23dis-Fc
HL-H-16415 µg/mi dis-Fc	0,0119 (0.0012)	0.0378 (0.0061)		0.0242 (0.0029) 53%	0.0172 (0.0031) 80%	0.0310 (0.0036) 26%
HL-H-155 9 µg/ml dis-Fc	0,0164 (0,0010)	0,0468 (0.0059).	0.0454 (0.0052) 5%	0.0412 (0.0107) 18%	0.0227 (0.0038) 79%	0,0207 (0,0015) 86%

¹ Slopes to average triplicate Y values and treat as a single data point in order to test whether the slopes are significantly

[0099] ADAM-20 and 23disk-Eppotypeptides showed the greatest inhibition of both EGF- and FMA-induced endothelial infigration at 15 a.p/ml. ADAM-15 and 17 disk-Fp otypeptides were less effective at inhibiting endothelial cell ingration at 15 a.p/ml. Hu lgG did not inhibite EGF- or PMA-induced endothelial cell migration in eny of the experiments performed where it was included as a control Fp optodism.

EXAMPLE 4

10

20

200

Activity of ADAM Disintegrin Domain Polypeptides in a Corneal Pocket Assay

[0100] A mouse comeal pocker assay is used to quantitate the inhibition of angiogenesis by ADAM dishintagrin-Fo polypeptides in vivo, in this assay, agents to be tested for angiogenic or anti-angiogenic activity are immobilized in a slow release form in a hydron pellet, which is implanted into micropockets created in the conneal epithellum of anesthetized mice. Vascularization is measured as the appearance, density, and extent of vessel ingrowth from the vascularized corneal imbus into the normally vascular connea.

[0101] Hydron pellets, as described in Kenyon et al., Invest Optimenol. & Visual Science 37, 1625, 1996, incorporate succellate with bFDEF (90 ng/bellet), bFDEF and IgG (11 µg/pellet, control), or bFDEF and a range of concentrations of ADAM distintegrin-Fc polypeptide. The pellets are surgically implanted into corneal stronal micropockets created by micro-dissection 1 mm netials to the lateral corneal limbus of 6-8 week old male CS78L mice. After five days, at the peak of neovescular responses to bFDEF, the corneas are photographed, using a 28tes sit imap, at an incipient angle of 55-50 from the polar axis in the meridian containing the pellet, Images are digitized and processed by subtractive color fitters (Adobe Photoshop 4.0) to delineate established microvessels by hemosploits occretif. Image analysis offware.

² Data in parentheses is the +/- standard error of slopes

³ Percent inhibition compared to migration rate observed in the presence of PMA

² Data in parentheses is the +/- standard error of slopes

³ Percent inhibition compared to migration rate observed in the presence of EGF alone

(Bioquant, Nashville, TN) is used to calculate the fraction of the corneal image that is vescularized, the vessel density within the vascularized area, and the vessel density within the total cornea. The inhibition of bFGF-induced corneal angiocenesis, as a function of the dose of ADAM disintentries to solvectified, is determined.

F EXAMPLE 5

inhibition of Neovascularization by ADAM Disintegrin Domain Polypeptides in a Murine Transplant Model

[0102] Survival of heterotopically transplanted cardiac tissue from one mouse atoms to the ear skin of another genetically similar mouse requires adequate necessualization by the transplanted near and the surrounding dissue, in promise survival and senergy for cerdiac muscle function, inadequate vasculature at the site of transplant causes excessive schemis to the heart, issue demange, and failities of the issues to engraft. Agents that antagonise factors involved in anotherisis of intrinsplant and vibrantely argraftment itself. A municiple cardiac isograft mode is used to demonstrate the antagonise factors involved in antagonistic effects of ADAM disintegrin-Fo polypeptides on neversacularization. Fermate BALEG c12 weeks of ago, recipients are given encentain heart grafts from donor miles of the same strain. The donor heart tissue is grafted into the left ear pinnes of the recipient on day 0 and the mice are divided into two groups. The control group receives human (sQ (ful sQ) while the other group receives ADAM disintegrin-Fo perplayebide, both intraperitionally. The treamments are continued for five consecutive days. The functionality of the grafts is determined by monitoring visible putselled extityle on days 7 and 14 post-engraftment. The inhibition of functional engraftment, as a function of the dose of ADAM disintegrin-Fo polypeptide, is determined by the transplanted hearts is examined is order to visualization the effects of ADAM disintegrin-Fo polypeptide, is determined by the transplanted hearts is examined is order to visualization the effects of ADAM disintegrin-Fo polypeptide, is determined by the transplanted hearts is examined is order to visualization the effects of ADAM disintegrin-Fo polypeptide, is determined by the transplanted hearts is examined is order to visualization the effects of ADAM disintegrin-Fo polypeptide is order to visualization the effects of ADAM disintegrin-Fo polypeptide.

EXAMPLE 6

Treatment of Tumors With ADAM Disintegrin Domain Polypeptides

[0103] ADAM disintegrin-Fc polypaptides are tested in animal models of solid tumors. The effect of the ADAM disintegrin-Fc polypaptides is determined by measuring tumor frequency and tumor growth.

[0104] The biological activity of ADAM disintegrin-Fc polypeptides is also demonstrated in other in vitro, ex vivo, and in vivo assays known to the skilled artisen, such as calcium mobilization assays and assays to measure platelet activation, recruitment, or activation and the properties of the pro

(916) The relevant disclosures of publications cited herein are specifically incorporated by reference. The examples presented above are not intended to be exhaustive or to firthit secope of the invention. The skilled artisar will uncerstant that variations and modifications and variations are possible in light of the above teachings, and such modifications and variations are intended to be within the scope of the invention.

Annex to the application documents - subsequently filed sequences listing

101061

40

35

80

SEQUENCE LISTING

\$	<110> Limmusex Corporation Ranslow, Millam C. Poindexter, Kurt Cerretti, Douglas P. Black, Roy A.
	<120> INTEGRIN ANTAGONISTS
10	<130> 2958-WO
	<140> <141>
13	<150> 60/184,865 <151> 2000-02-25
	<160> 22
	<170> PatentIn Ver. 2.2
26	<210> 1 <211> 1700 <212> 17NA <713> Artificial Sequence
26	<220> <223> Description of Artificial Sequence: fusion polypoptide
300	<220s <221s CDS <222s (118)(1602) <400s 1
	gggttttccc agtcacgacg ttgtaamacg acggccagtg aattgtmata cyactcacta 60
WAT .	tagggcqaat tgggtaccgg gcccccctc gaggtcgacc caagctggct agccacc 117
36	atg gag aca gac aca ctc ctg cta tgg gta ctg ctg ctc tgg gtt cca Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro 1 5 10
	ggt too act ggt act agt tgt ggg aac ctg tit gtg gag cgt ggg gag 21: Gly Ser Thr Gly Thr Ser Cys Gly Asn Leu Phe Val Glu Arg Gly Glu
40	20 25 30
	cag tgc gac tgc gqc ecc ecc gag gac tgc egg aac ege tgc tgc aac 26: Gln Cya Asp Cya Gly Pro Pro Glu Asp Cya Asp Asp Cya Cya Asn 40
45	tet acc acc tgc cag etg get gag ggg gcc cag tgt geg cac ggt acc lot far Thr Cys Gln Leu Ala Glu Gly Ala Gln Cys Ala His Gly Thr 5 60 55
50	tgc tgc cag gag tgc aag gtg aag ccg gct ggt gag ctg tgc cgt ccc Cys Cys Gln Glu Cys Lys Val Lys Pro Ald Sly Glu Leu Cys Arg Pro 65 70 88
	aag aag gac atg tgt gac ote gag gag tte tgt gac ggc egg cac eet 40° Lys Lys Asp Met Cys Asp Leu Glu Glu Phe Cys Asp Gly Arg His Pro 85
88	gag tgc dog gas gad goe ble dag gag asd ggd sog dod tgc bed ggg 450

	Glu	Cys	Pro	Glu 100	Asp	Ala	Phe	Gln	Glu 105	Asn	CJA	Thr	Pro	Cys 110	Ser	Gly	
5													cag Gln 125				501
10													tec Ser				549
	tat Tyr 145	gac Asp	atc	cta Leu	eca Pro	ggc Gly 150	tgc 'Cys	aag Lys	gcc Ala	agc Ser	rg Arg	cac Tyr	agg Arg	gct Ala	gac Asp	Met 160	597
15													tta Leu				645
20													gag Glu				693
													Pro 205				741
25													aga Arg				789
36													cac His				837
													gcg				885
35													asa Lys				933
40				Cys									ecg Pro 285				981
			Pro					Asp					Ser				1029
46	9ag Glu 305	Val	Thr	tgc Cys	gtg Val	geg Val 310	gtg Val	gac	gtg Val	Ser	His 315	gae Glu	gac	Pro	gag Glu	gtc Val 320	1077
50	aag Lys	Phe	aac Asn	tgg Trp	Tyr 325	Val	gac	Gly	gtg Val	gag Glu 330	Val	Cat	aat Asn	gcc	aag Lys 335	Thr	1125
294	aag Lys	Pro	egg Arg	gag Glu 340	Glu	cag Gln	tac	aac Asn	ago Ser 345	acg	tac Tyr	cgt Arg	gtg Val	gtc Val 350	agc Ser	gtc Val	1173
58	Leu	Thr	yal yal 355	Leu	cac His	cag Gln	Asp	tgg Trp 360	Leu	aat	Gly	aag Lys	gag Glu 365	Tyr	aag Lys	tgc Cys	1221

	aag gto Lys Val	Ser	aac Asa	asa Lys	gcc	Leu	cca Pro	gcc Ala	ece Pro	ate	Glu	aaa Lys	ace Thr	atc Tle	Ser	1269
	376					375					380					
5	saa gcc	aaa	999	cag	ccc	cās	gaa	cca	cag	gtg	tac	acc	ctg	ccc	aca	1317
	Lys Ala	rys	gry.	Glm	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro		~
	385				390					395					400	
	tec con	man	man	atra	200	= 0.0	200	~~~	ata	200	*****				andr as	1365
	Ser Arg	GTo	nio	Mar	The	Eare	age	Gin	Qu'i	For	roo	acc.	Ege	tou	gec	1202
	202 1419		W. W.	405	****	r.3 ro	rane	0430	410	acr	Den	1 41.0	cys	415	VIXI	
10				***					****					***		
	aaa ggc	tte	tat	ccc	agc	gac	atc	gcc	gtg	gag	tgq	gag	age	aac	dad	1413
	bys Gly	Phe	Tyr	Pro	Ser	Asp	Tie	Ala	Val	Glu	Trp	Glu	Sex	Asn	Gly	
			420					425					430			
15	cag ccg	gag	aac	aac	tac	aag	acc	acg	cck	ccc	gtg	cçê	gac	tec	gac	1461
	Gin Pro	435	8311	MEST	TAL	ràs	640	rnr	52.0	PEO	VRI	445	Asp	ser	Asp	
		46.5 (5					440					442				
	ggc tcc	ttc	ttc	ctc	tat	age	aau	ctc	acc	ate	gac	aan	age	agn	ton	1509
	Gly Ser	Phe	Phe	Leu	Tyr	Sex	Lys	Leu	Thr	Val	Asp	Lvs	Ser	Are	Tro	
	450	1				455					460					
20																
	cag cag	a aaa	aac	gtc	tte	tea	tgc	tcc	ara	atg	Cat	gag	get	crg	cac	1557
	Gln Glr 465	rera	esn.	487	470	Ser	Lys	ser	var		Hilb	GIG	Aie	Leu		
	90.5									475					480	
	88C C80	tac	acq	caq	aaq	age	ctc	tac	cta	tet	cca	cat	aaa	tida		1602
25	Asn His	Tyr	Thr	Gla	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	ugu		
				485					490			-		495		
	actagaç	icea .	ccac	cacc	gc 99	3£39	aget	c ca	getti	ttgt	5000	es suc	age s	និងជីជិន	gttaat	1662
	ttcgago	*****	mart.		40 m	***		h ashi								1700
.902	cocgação	accs :	uruu	20.00	ac gr	4 (.4.20)	rage:	. yc	LUCE	r G						1700
.907																
	<210> 2															
	<211> 4															
	<212> 1															
	<213> 2						-2-4	~								
36	<223> 1	olyp			r Mr.	CACA	cra.	ped	aence	9; E	1210	3				
		J	-p	-												
	<\$00> 2															
	Met Glu	Thr	Asp	The	Leu	Leu	Leu	Trp		Leu	Leu	Leu	Trp	Val	Pro	
	a 1 .			5	_				3.0					15		
40	Gly Ser	THE	20	Thr	ser	Çys	GIA	ASR 25	Leu	Phe	Val	Clu	Arg	Gly	Glu	*
	Gln Cys	a Aem		G127	pro	Dro	6311		men	0.00	***	Name	20	Chem	A mare	
	uz	35	~,,	023		***	40	nop	Cys	wra	A STATE A	45	cys	Cys	Pesses	
	Ser Thi		Cvs	Gln	Lou	Ala		GIV	Ala	Gin	Cure		Nie	Giv	war	
	50	3				55					60	*****	10.0.00	,	****	
45	Cys Cys	Gln	Glu	Cys	Lys	Va3	Lys	Pro	Ala	Gly	Glu	Leu	Cys	Arg	Pro	
40	65				70					75					80	
	bys by:	a Asp	Met	Cys	Asp	Leu	Glu	Glu		Суs	Asp	Gly	Arg		Pro	
				85					98					95		
	Glu Cyr	Fro	100	qaa	ALA	Pne	Gin	Glu	Asn	GIÀ	Thr	Pro	CAS	Set	Gly	
	Oly my	con		Ann	Clar	A7.	C++0	105	m	v		m2	110		C17	
50	Gly Ty	115	137	MISTE	OLY	W.T.W	120	Pro	ane	ren	Ata	125	GER	Cys	GIU	
			01	Pro	Glv	Glv	Gin	Ala	Ala	ela	G) n		CV.	Pho	Ser	
	Ala Phi	a Trn														
	Ala Pho	3				135					140					
	3.34	3				135					140					
	13: Tyr Asi 145) 7 Ile	Leu	Pro	Gly 150	Cys	Lys	Ala	Ser	Arg 155	140 Tyr	Arg	Ala	Asp	Met 160	
66	Tyr Ası) 7 Ile	Leu	Pro Gln	Gly 150 Cys	Cys	Lys	Ala	Ser Gln	Arg 155	140 Tyr	Arg	Ala	Asp Arg	Met 160	
66	13: Tyr Asi 145) 7 Ile	Leu	Pro	Gly 150 Cys	Cys	Lys	Ala	Ser	Arg 155	140 Tyr	Arg	Ala	Asp	Met 160	

```
lle Cys Ile Val Asp Val Cys His Ala Leu Thr Thr Glu Asp Gly Thr
                     180
                                         185
                                                             190
          Ala Tyr Glu Pro Val Pro Glu Gly Thr Arg Cys Gly Pro Glu Lys Val
                 195
                                     200
                                                        205
          Cys Trp Lys Gly Arg Cys Gln Asp Leu His Val Tyr Arg Ser Ser Asn
                                215
                                                     220
         Cys Ser Ala Gln Cys His Asn His Gly Val Cys Asn His Lys Gln Glu
225 230 235
          Cys His Cys Bis Ala Gly Trp Ala Pro Pro His Cys Ala Lys Leu Leu
                         245
                                           250
                                                                255
          Thr Glu Val His Ala Ala Ser Gly Arg Ser Cys Asp Lys Thr His Thr
                     260
                                         265
                                                            270
          Cys Pro Pro Cys Pro Ala Pro Clu Ala Glu Gly Ala Pro Ser Val Phe
                 275
                                     280
                                                        285
          Les Phe Pro Pro Lys Pro Lys Asp Thr Les Met Ile Ser Arg Thr Pro
             290
                                 295
                                                    300
          Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
                             310
                                              315
          Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
          Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
                     340
                                         345
                                                            350
          Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
20
                                     360
                 355
                                                        365
          Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
             370
                                 375
                                                     380
          Lys Ale Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
                             390
                                                 395
          Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
                         405
                                           410
          Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
                                       425
                                                             430
          Gin Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                 435
                                     440
                                                        445
          Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
30
                                 455
                                                    460
          Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Lou His
                            470
                                               475
          Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                         485
                                             490
35
          <210> 3
          <211> 1668
          <212> DNA
          <213> Artificial Sequence
40
          <220>
          <223> Description of Artificial Sequence: fusion
               polypeptide
          <2205
          <221> CDS
          <222> (46) .. (1647)
          ggtacceggc cocccctcga ggtcgaccca agctggctag ceacc atq qaq aca qac 57
                                                           Met Glu Thr Asp
          aca etc etg eta tgg gta etg etg etc tgg gtt eca ggt tec act ggt
                                                                           105
          Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro Gly Ser Thr Gly
           8
                              3.0
         act agt tgt ggt aat aag ttg gtg gac get ggg gaa gag tgt gac tgt
```

	Thr	Ser	Cys	Gly	Asn 25	Lys	Leu	Va1	Asp	Ala 30	Gly	Glu	Glu	Cys	Asp 35	Cys	
.5	Gly	act Thr	eca	aag bys 40	gaa Glu	tgt Cys	gaa Glu	ttg Leu	gac Asp 45	ect Pro	tgc Cys	tgc Cys	gaa Glu	gga Gly S0	agt Ser	acc	201
10	tgt Cys	gag gag	ctt Leu 55	aaa Lys	tca Ser	ttt Phe	gct Ala	gag Glu 60	tgt Cys	gca Ala	tat Tyr	gly	gac Asp 65	tgt Cys	tgt Cys	aae Lys	249
	gac Asp	tyt Cys 70	egg. Arg	ttc Phe	ctt beu	cca Pro	gga Gly 75	Gly	act Thr	tta Leu	tgc Cys	cga Arg 80	Gly gga	aaa Lys	Thr	agt Ser	297
15	gag Glu 85	tgt Cys	gat Asp	gtt Val	eca Pro	gag Glu 90	tac Tyr	tgc Cys	aat Asn	ggt Gly	Ser 95	tct Ser	cag Gln	ttc Phe	ty:	Gin 100	345
80	Pro cca	gat	gtt Val	ttt	att 11e 105	cag Gln	aat Asn	gga Gly	tat Tyr	Pro 110	Cys	Gln	aat Asn	aac Asn	aaa Lys 115	gcc Ala	393
20	tat Tyr	tge Cys	tac Tyr	aac Asn 120	ejà âàc	atg Net	tgc Cys	Cag Gla	tat Tyr 125	tat Tyr	gat Asp	gct Ale	caa Gln	tgt Cys 130	caa GIn	gtc Val	441
25	11.e	Phe	Gly 135	Ser	Lys	Ala	aag Lys	Ala 140	Ala	Pro	Lys	Asp	Cys 149	Phe	Tle	Glu	489
	gtg Val	Asn 150	tet	caa Lys	gly	gac	aga Arg 155	trt. Phe	Gly Gly	aat Asn	tgt Cys	ggt Gly 150	ttc Phe	tet Ser	Gly	aat. Asn	537
30	gaa Glu 165	Tyr	rys	aag Lys	tgt Cys	gcc Ala 170	act	61 A 888	aac Asn	gct	ttq Leu 175	tgt Cys	gga Gly	aag Lys	cct Leu	cag Gln 180	585
35	tgt Cys	gag Glu	Asn	gta Val	Gln 185	Gin	ata Lle	Pro	gta Val	ttt Phe 190	gga Gly	att lle	gtg Val	ect Pro	get Ala 195	att Ile	633
	Ile	Gln	Thr	Pro 290	agt Ser	Arg	ggc Gly	Thr.	aaa Lys 205	tgt Cys	tgg Trp	ggt Gly	gtg Val	gat Asp 210	ttc Phe	Gln	681
40	cta Leu	gga Gly	tea Ser 215	gat	gtt Val	Pro	gat Asp	Pro 220	GJA 888	atg Met	gtt Val	aac	gaa Glu 225	Gly	aca Thr	ase Lys	729
45	tgt Cys	99t Gly 230	gct Ala	gga	aag Lys	atc	tgt Cys 235	aga Arg	aac Asn	ttc Phe	cag Gln	tgt Cys 240	gta Val	gat Asp	gct Ala	tet Ser	777
	gtt Val 245	Leu	ant Asn	tat	gac	tgt Cys 250	gat. Asp	gtc Val	cag Gln	aaa Lys	aag Lys 255	tgt Cys	cat His	gga Gly	cat His	999 61y 260	825
50	gta Val	tgt Cys	aat. Asn	agc	aat Asn 255	Lys	aat Asn	tgt Cys	cac His	tgt Cys 270	gaa Glu	aat Asn	gg: Gly	tgg Trp	gct Ala 275	Pro	873
56	eca Pro	aat. Asn	tgt Cys	gag Glu 280	act Thr	Lys	gga Gly	tac Tyr	gga Gly 285	gga Gly	agt Ser	gtg Val	gac Asp	agt Ser 290	gga Gly	cet Pro	921

	aca tac	aat gaa	arg aat	act gca	ttg age	gae gga	tot tat	gac aaa	969
		Asn Glu 295			Leu Azg				
S	act cac Thr Bis 310	aca tgc Thr Cys	cca ecg Pro Pro	tgc cca	gca cct	gaa gec Olu Ala 320	dad ode	gcg ccg Ala Pro	1017
10	tca gic Ser Val 325	tte ete Phe Leu	ttc ecc Phe Pro 330	cca aaa Pro Lys	ecc aas Pro Lys	gac acc Asp Thr 335	ctc atg Lew Met	atc tcc Tle Ser 340	1065
15	ogg acc Arg Thr	cct gag Pro Glu	gtc aca Val Thr 345	tgc gtg Cys Val	gtg gtg Val Val 350	Asp Val	age cac Ser His	gam gac Glu Asp 355	1113
	cet gag Pro Glu	gtc aag Val Lys 360	ttc aac Phe Asn	tgg tac Trp Tyx	gtg gad Val Ası 365	ggc gtg Gly Val	gag gtg Glu Val 370	cat eat His Asn	1151
20	Ala Lys	aca aag Thr Lys 375	ecg agg Pro Arg	gag gag Glu Glu 380	cag tag Gln Tys	asc ago Asn Ser	acg tac Thr Tyr 385	egg gtg Arg Val	1209
25	gtc agc Val Ser 390	gtc ctc Val Leu	acc gtc Thr Val	ctg cac Les His 395	Gln Asi	tgg ctg Trp Leu 400	aat ggc Asn Gly	aag gag Lys Glu	1257
	tac aag Tyr Lys 405	tgc aag Cys Lys	ytc tcc Val Ser 410	aac aaa Asn Lys	gee etc Ala Leu	Pro Ala 415	pro Ile	gag aaa Glu Lys 420	1305
.30	sec etc Thr Ile	toc aaa Ser Lys	gcc aaa Ala Lys 425	ggg cag Gly Gln	Pro Arg	Glu Pro	cag gtg Gln Val	tac acc Tyr Thr 435	1353
	ctg ccc Leu Pro	eca tec Pro Ser 440	ogg gat Arg Asp	gag ctg Glu Leu	acc ass Thr Lys	aac cag Asn Gln	gtc agc Val Ser 450	ctg acc Leu Thr	1401
36	tge etg Cys Leu	gtc aaa Val Lys 455	ggo tto Gly Phe	tat ccc Tyr Pro 460	age gad Ser Asi	atc gcc Tle Ala	gtg gag Val Glu 465	tgg gag Trp Glu	1449
40	agc aat Ser Asn 470	ggg cag Gly Gln	ccg gag Pro Glu	aec aac Asn Asn 475	tac ass Tyr Lys	acc acg Thr Thr 480	ect ccc Pro Pro	gtg ctg Val Leu	1497
45	gac tcc Asp Ser 485	gac ggc Asp Gly	Ser Phe 490	Phe Leu	tac ago Tyr Ser	ang ctc bys Leu 495	acc gtg Thr Val	gac aag Asp Lys 500	1.545
	agc agg Ser Arg	tgg cag Trp Gln	cag ggg Gln Gly 505	asc gtc Asu Val	tto tos Phe Ser 510	Cys Ser	gtg atg Val Met	cat gag His Glu 515	1593
80	get etg Ala beu	cac aac Ris Asn 520	cac tac His Tyr	acg cag Thr Gln	ang ago Lys Sex 525	ctc tcc Leu Ser	ctg tct Leu Ser 530	ccg ggt Pro Gly	1641
	aan tga Lys	actagage	ogg cogc	tacaga t					1668

<210× 4

<211> 533

20

25

90

45

<212> PRT <213> Artificial Sequence

<223> Description of Artificial Sequence: fusion

polypeptide

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Thr Ser Cys Gly Asn Lys Leu Val Asp Ala Gly Glu 20 25 30 Glu Cys Asp Cys Gly Thr Pro Lys Glu Cys Glu Leu Asp Pro Cys Cys 35 40 45 Glu Gly Ser Thy Cys Lys Leu Lys Ser Phe Ala Glu Cys Ala Tyr Gly
50 55 60 Asp Cys Cys Lys Asp Cys Arg Phe Leu Pro Gly Gly Thr Leu Cys Arg Gly Lys Thr Ser Glu Cys Asp Val Pro Glu Tyr Cys Asn Gly Ser Ser 85 90 95 Gln Phe Cys Gln Pro Asp Val Phe Ile Gln Asn Gly Tyr Pro Cys Gln 105 Asn Asn Lys Ala Tyr Cys Tyr Asn Gly Met Cys Gln Tyr Tyr Asp Ala 115 120 125 Gln Cys Gln Val Ile Phe Gly Ser Lys Ala Lys Ala Ala Pro Lys Asp 130 135 Cys Phe Ile Glu Val Asn Ser Lys Gly Asp Arg Phe Gly Asn Cys Gly 145 150 160 Fine Ser Gly Asn Glu Tyr Lys Lys Cys Ala Thr Gly Asn Ala Leu Cys 165 170 175 165 Gly Lys Leu Gln Cys Glu Asn Val Gln Glu Ile Pro Val Phe Gly Ile 180 185 190 Val Pro Ala Ile Ile Gln Thr Pro Ser Arg Gly Thr Lys Cys Trp Gly 195 Val Asp Phe Gln Leu Gly Ser Asp Val Pro Asp Pro Gly Met Val Asm 210 215 220 Glu Gly Thr Lys Cys Gly Ala Gly Lys Ile Cys Arg Asn Phe Glu Cys 225 230 235 Val Asp Ala Ser Val Leu Asn Tyr Asp Cys Asp Val Gln Lys Lys Cys 245 250 255 His Gly His Gly Val Cys Asn Ser Asn Lys Asn Cys His Cys Glu Asn 260 265 270 Gly Trp Ala Pro Pro Asn Cys Glu Thr Lys Gly Tyr Gly Ser Val 275 280 285 Asp Ser Gly Pro Thr Tyr Asm Glu Met Asm Thr Ala Leu Arg Asp Gly 290 295 300 Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala 305 316 319 320 Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thx 325 330 Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val 340 345 . 350 Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val 355 360 365 Glu Val His Asn Ale Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser 370 380 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu 390 395 Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala 405 410 415 Pro Ile Giu Lys Thr Tie Ser Lys Ala Lys Gly Gln Pro Arg Giu Pro 420 430 Gln Val Tyr Thr Len Pro Pro Ser Arg Asp Gln Len Thr Lys Asm Gln 435 440 Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala 455 450

		Val Glu Trp Glu Ser Asn Gly Gln Pro Glo Asn Asn Tyr Lys Thr Thr 465 470 475 480	
		Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu 485 490 495	
	5	Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val The Ser Cys Ser	
		Val Met His Glu Ala Leu His Asn His Tyr Thr Glo Lys Ser Leu Ser 515 526 525	
		Leu Ser Pro Gly Lys	
	10		
		<210> 5 <211> 1443	
		<212> DNA	
	15	<213> Artificial Sequence	
		<220b <223> Description of Artificial Sequence: fusion polypoptide	
		<220>	
	90	<221> CDS <222> (25)(1422)	
		<400> % gregatoress getggetage care stg gag are gat are etc etg eta tgg	51
	25	Mot Glu Thr Asp Thr Leu Leu Trp	27
	ಣ		
		gta etg etg etc tgg gtt eea ggt tee aet ggt aet agt egt gga aat Val Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Thr Ser Cys Gly Aan 10 25	99
	90	gas atg gta gas cas ggt gas gas tgt gat tgt ggc tat agt gac cag Gly Met Val Glu Glu Glu Cys Asp Cys Gly Tyr Ser Asp Glu 30 35 40	147
		tgt ama gat gam tgc tgc ttc gat gca amt cam cca gag ggm ama ama Cys Lys Asp Glu Cys Cys Phe Asp Ala Asn Gln Pro Glu Gly Arg Lys	195
	35	***	
		tgc aas etg aas ect ggg aas cag tgc agt cca agt cas ggt ect tgt Cys Lys Leu Lys Pro Gly Lys Gin Cys Ser Pro Ser Gin Gly Pro Cys 60 70	243
	40	tgt ace gca cag tgt gca ttc ang tca ang tct gag ang tgt cgg gat	291
		Cys Thr Ala Gln Cys Ala Phe Lys Ser Lys Ser Glu Lys Cys Arg Asp 75 80 85	
		gat toa gad tgt goa agg gaa gga ata tgt aat ggo tto aca got oto	339
	15	Asp Ser Asp Cys Ala Arg Glu Gly Ile Cys Asm Gly Phe Thr Ala Leu 90 95 100 105	
		tgc cca gca tot gac cer asa cca asc tte aca gac tgt aat agg cat	387
		Cys Pro Ala Ser Asp Pro Lys Pro Asn Phe Thr Asp Cys Asn Arg His 110 115 120	
á	92	aca cas gtg tgc att aat ggg cas tgt gca ggt ter ate tgt gag aas	435
		Thr Glm Val Cys Ile Asm Gly Glm Cys Ala Gly Ser Ile Cys Glu Lys 125 130 135	
		tat ggc tta gag gag tgt acg tgt gcc agt tct gat ggc aaa gat gat	483
	55	Tyr Gly Leu Glu Glu Cys Thr Cys Ala Ser Ser Asp Gly Lys Asp Asp 140 145 150	

	aaa	gaa	tta	rgc	cat	gta	tgc	tgt	atg	aag	aaa	atg	gac	CCS	t.ca	act	531
	Lys	Glu 155	Leu	Cys	Hís	Val	Cys 160	Cys	Met	Lys	Lys	Met 165	Asp	Pro	Ser	Thr	
5	tgt Cys 170	gcc Ala	agt. Ser	aca	GJ Å 333	tet Ser 175	gtg Val	cag Gln	tgg Trp	agt Ser	agg Arg 180	cac His	ttc Phe	agt Ser	ggt	cga Arg 185	579
10		atc															627
16	tgt Cys	gat Asp	gtt Val	ttc Phe 205	atg Met	Arg cgy	tgc Cys	aga Arg	tta Leu 210	gta Val	gat Asp	ger Ala	gat Asp	ggt Gly 215	cct Pro	cta Leu	675
10		agg															723
20	get Ala	gaa Glu 235	aga Arg	tot Ser	tgt Cys	gac	asa Lys 240	act	cac His	aca Thr	tgc Cys	oca Pro 245	ccg Fro	tgc Cys	Pro	gca Ala	771.
		gaa Glu															819
25	aag Lys	gac	ace	cec Leu	atg Met 270	atc Tle	tec	Arg	acc Thr	cct Pro 275	gag Glu	gtc Val	aca Thr	tgc Cys	gtg Val 280	gtg Val	867
30	gtg Val	gac	gtg Val	agc Ser 285	cac His	gaa Glu	gac	cct Pro	gag Glu 290	gtc Val	aag Lys	tto Phe	aac Asn	tgg Trp 295	tac Tyr	gtg Val	915
	gac Asp	gge	gtg Val 300	gag Glu	gtg Val	cat His	aat Asn	gcc Ala 305	aag Lys	aca Thr	aag Lys	ecg	egg Arg 310	gag Glu	gag Glu	cag Gln	963
36	tac Tyr	aac Asn 315	Ser	acg	tac Tyr	Arg	gtg Val 320	Va1	agc Ser	gtc Val	ctc Leu	acc Thr 325	gtc Val	Leu	cac His	cag Gln	1011
40		tgg Trp					Glu					Val					1059
		Pro															1107
45		gaa Glu			Val												1155
500	aag Lys	aac	Gln 380	Val	ago	ctg	acc	Cys 385	Leu	gtc Val	aaa Lys	Gly ggc	ttc Phe 390	tat	Pro	agc Ser	3.203
		ate 11e 395	Ala					Ser									1351
36	aag	acc	acg	cct	ccc	gtg	ctg	gac	tec	gac	gge	tec	tte	ttc	ctc	tac	1299

	Lys Thr 410	Thr	Pro	Pro	Val. 415	Leu	Asp	Ser	Asp	Gly 420	Ser	Phe	Phe	Leu	Tyr 425	
δ	agc and Ser Lys	ctc Leu	Lpx	gtg Val 430	gac Asp	aag Lys	agc Ser	agg	tgg Trp 435	cag Gln	cag Gln	Gly	aac Asn	gtc Val 440	tt <i>c</i> Phe	13
	tea tac	ron	oto	are	car	ran r	ect		~~~	220	020	+==	200		220	13
	tea tge Ser Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	Nis	Tyr	Thr	Gin	Lvs	1.3
10			445					450					455		- 4 -	
	age ete	her	ntn	tat	cen	aar	***	***								14
	Ser Leu	Ser 460	Leu	Ser	Pro	Gly	Lys 465	cya	acca	.gayı	.gg (.cyc.	Lavas	зас		1.0
5	<210> 6 <211> 4 <212> F	55														
	<213> A															
	<223> E	escri			art	ilEi(caal	280	16UC	e: It	sios	3				
513	_			-												
	<400> 6 Met Glu		Non	When	You	7 01-	r	Maria	tro 7	t a	T	Y	mass	11-1	F	
	1	. 4444	rap	5	ner	A) WG	Literu	2 3.30	10	Deu	Leu	roes.	art	15	PLO	
NS	Gly Sex		36					25					30			
	Glu Cys	35	Cys	era	3Az	Ser	Asp 40	Gin	CAs	Lys	Asp	Glu	Cys	CAR	Phe	
	Asp Ala	Asn	Gln	Pro	Glu	Gly 55		Lys	Cys	Lys	Leu 60	Lys	Pro	Gly	Lys	
	Gln Cys	Ser	Pro	Ser	Gln	Gly	Pro	Cys	Cys		Ala	Gln	Cys	Ala		
ký	65 Lys Sex	Time	Car	Gin	.70	Cor	***	aen	Ann	75	n-m	~~	81.0	Xvor	90	
	070 001	240	CHOIA	85	 3	cya	Yar 9	Nap	90	246 2	Note	Cys	MARK	95	orn.	
	Gly Ile		100					105					110			
	Pro Asr	1 Phe	Lux	Asp	Cys	asn	Arg 120	His	Thr	Gln	Val	Cys 125	Tle	Asn	Gly	
5	Gln Cys 130	Ala	Gly	Ser	Ile	Cys 135		Lys	Tyr	Gly	Leu 140		Glu	Cys	Thr	
	Cys Ala 145	Ser	Ser	Asp	Gly	Lys	Asp	Asp	Lys		Leu	Cys	His	Val		
															1.60	
		TAR	Yes	Met	150 Asn	pro	Ser		Cve	155	Ser	Thr	Cla	Sar		
	Cys Met			165	Asp			Thr	1.70	Ala				175	Va1	
ıa	Cys Met Gln Tr	Ser	Arg 180	165 His	Asp	Ser	Gly	Thr Arg 185	170 Thr	Ala	Thr	Leu	Gln 190	175 Pro	Val Gly	
16	Cys Met	Ser Cys	Arg 180	165 His	Asp	Ser	Gly Gly	Thr Arg 185	170 Thr	Ala	Thr	Leu Phe	Gln 190	175 Pro	Val Gly	
e e	Cys Met Gln Tr	Ser Cys 195	Arg 180 Asn	165 His Asp	Asp Phe Phe	Ser Arg	Gly Gly 200	Thr Arg 185 Tyr	170 Thr Cys	Ala Ile Asp	Thr Val Leu	Leu Phe 205	Gln 190 Het	175 Pro Arg	Val Gly Cys	
	Cys Met Gin Tr; Ser Pro Arg Let 210 Phe Ses 225	Cys 195 1 Val	Arg 180 Asn Asp Glu	165 His Asp Ala Leu	Asp Phe Phe Asp Tyr 230	Ser Arg Gly 215 Glu	Gly 200 Pro Asn	Thr Arg 185 Tyr Leu Ile	170 Thr Cys Ala Ala	Ala Ile Asp Arg Glu 235	Thr Val Leu 220 Arg	Leu Phe 205 Lys Ser	Gln 190 Met Lys Cys	175 Pro Arg Ala Asp	Val Gly Cys Ile Lys 240	
	Cys Met Gin Try Ser Pro Arg Let 210 Phe Ses	Cys 195 1 Val	Arg 180 Asn Asp Glu	165 His Asp Ala Leu Pro	Asp Phe Phe Asp Tyr 230	Ser Arg Gly 215 Glu	Gly 200 Pro Asn	Thr Arg 185 Tyr Leu Ile	170 Thr Cys Ala Ala Pro	Ala Ile Asp Arg Glu 235	Thr Val Leu 220 Arg	Leu Phe 205 Lys Ser	Gln 190 Met Lys Cys	175 Pro Arg Ala Asp Ala	Val Gly Cys Ile Lys 240	
	Cys Met Gin Tr; Ser Pro Arg Let 210 Phe Ses 225	Cys 195 195 1 Val	Arg 180 Asn Asp Glu Cys Leu	165 His Asp Ala Leu Pro 245	Asp Phe Phe Asp Tyr 230 Pro	Ser Arg Gly 215 Glu Cys	Gly 200 Pro Asn Pro	Thr Arg 185 Tyr Leu Ile Ala Pro	170 Thr Cys Ala Ala Pro 250	Ala Ile Asp Arg Glu 235 Glu	Thr Val Leu 220 Arg Ala	Phe 205 Lys Ser Glu	Gln 190 Met Lys Cys Gly Met	Arg Ala Asp Ala 255	Val Gly Cys Ile Lys 240 Pro	
s	Cys Met Gin Try Ser Pro Arg Let 210 Fhe Ses 225 Thr His	Ser Cys 195 Val Pro Thr	Arg 180 Asn Asp Glu Cys Leu 260	Asp Ala Leu Pro 245 Phe	Asp Phe Phe Asp Tyr 230 Pro	Ser Arg Gly 215 Glu Cys Pro	Gly 200 Pro Asn Pro Lys	Thr 185 Tyr Leu Ile Ala Pro 265	170 Thr Cys Ala Ala Pro 250 Lys	Ala Ile Asp Arg Glu 235 Glu Asp	Thr Val Leu 220 Arg Ala Thr	Leu Phe 205 Lys Ser Glu Leu	Gln 190 Met Lys Cys Gly Met 270	Arg Ala Asp Ala 255 Ile	Val Gly Cys Ile Lys 240 Pro Ser	
s	Cys Met Gin Try Ser Pro Arg bet 21(Fhe Ser 225 Thr His Ser Val	Ser Cys 195 Val Pro Thx Phe Pro 275	Arg 180 Asn Asp Glu Cys Leu 260 Glu	165 His Asp Ala Leu Pro 245 Phe Val	Asp Phe Phe Asp Tyr 230 Pro Pro	Ser Arg Gly 215 Glu Cys Pro	Gly 200 Pro Asn Pro Lys Val 280	Thr Arg 185 Tyr Leu Ile Ala Pro 265 Val	170 Thr Cys Ala Ala Pro 250 Lys Val	Ala Ile Asp Arg Glu 235 Glu Asp	Thr Vel Leu 220 Arg Ala Thr	Leu Phe 205 Lys Ser Glu Leu Ser 285	Gln 190 Het Lys Cys Gly Met 270 His	Arg Ala Asp Ala 255 Ile Glu	Val Gly Cys Ile Lys 240 Pro Ser Asp	
s	Cys Met Gin Try Ser Pro Arg Let 210 Fhe Ser 225 The His	Ser Cys 195 Val Pro Thx Phe Pro 275 Val	Arg 180 Asn Asp Glu Cys Leu 260 Glu	165 His Asp Ala Leu Pro 245 Phe Val	Asp Phe Phe Asp Tyr 230 Pro Pro	Ser Arg Gly 215 Glu Cys Pro	Gly 200 Pro Asn Pro Lys Val 280	Thr Arg 185 Tyr Leu Ile Ala Pro 265 Val	170 Thr Cys Ala Ala Pro 250 Lys Val	Ala Ile Asp Arg Glu 235 Glu Asp	Thr Vel Leu 220 Arg Ala Thr	Leu Phe 205 Lys Ser Glu Leu Ser 285	Gln 190 Het Lys Cys Gly Met 270 His	Arg Ala Asp Ala 255 Ile Glu	Val Gly Cys Ile Lys 240 Pro Ser Asp	
s	Cys Met GIn Try Ser Pro Arg Let 211 Phe Ser 225 Thr His Ser Val Arg Thr Pro Gin 294 Ala Lys	Ser Cys 195 Val Pro Thr Pro 275 Val	Arg 180 Asn Asp Glu Cys Leu 260 Glu Lys	165 His Asp Ala Leu Pro 245 Phe Val Phe	Asp Phe Phe Asp Tyr 230 Pro Pro Thr Asn	Ser Arg Gly 215 Glu Cys Pro Cys Trp 295	Gly 200 Pro Asn Pro Lys Val 280 Tyr	Thr Arg 185 Tyr Leu Ile Ala Pro 265 Val	176 Thr Cys Ala Ala Pro 250 Lys Val	Ala Ile Asp Arg Glu 235 Glu Asp Asp Gly	Thr Val Leu 220 Arg Ala Thr Val Val 300	Leu Phe 205 Lys Ser Glu Leu Ser 285 Glu	Gln 190 Met Lys Cys Gly Met 270 His	Arg Ala Asp Ala 255 Ile Glu His	Val Gly Cys Ile Lys 240 Pro Ser Asp Asn Val	
16 16	Cys Met GIn Try Ser Pro Arg Let 21(Fhe Ser 225 Thr Hix Ser Val Arg Thr Pro Gil	Ser Cys 195 Val Pro Thx Phe 275 Val Thx	Arg 180 Asn Glu Cys Leu 260 Glu Lys	165 His Asp Ala Leu Pro 245 Phe Val Pro	Asp Phe Fhe Asp Tyr 230 Pro Pro Thr Asn Arg 310	Ser Arg Gly 215 Glu Cys Pro Cys Trp 295 Glu	Gly 200 Pro Asn Pro Lys Val 280 Tyr	Thr Arg 185 Tyr Leu Ile Ala Pro 265 Val Val Gln	176 Thr Cys Ala Ala Pro 250 Lys Val Asp	Ala Ile Asp Arg Glu 235 Glu Asp Asp Gly Asp	Thr Vel Leu 220 Arg Ala Thr Val Val 300 Ser	Leu Phe 205 Lys Ser Glu Leu Ser 285 Glu Thr	Gln 190 Het Lys Cys Gly Met 270 His Val	Arg Ala Asp Ala 255 Ile Glu His Arg	Val Gly Cys Ile Lys 240 Pro Ser Asp Asn Val	

```
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                          340
                                                   345
                                                                           350
            Thr Ile Ser Lys Alo Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
                                              360
                                                                      365
            Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
                 370
                                         375
            Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                                    390
                                                            395
            Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
                              405
                                                       410
            Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
30
                          420
                                                   425
                                                                            430
            Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
                     435
                                             440
                                                                      445
            Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                                          455
                                                                450
            465
            <210> 7
            <211> 1638
            <212> DNA
580
            <213> Artificial Sequence
            <223> Description of Artificial Sequence: fusion
                   polypeptide
            <220>
            <221> CDS
            <222> (41) . (1609)
            ogggcoccc ctegaggteg acccaagetg gotagccacc atg gag ace gac aca
                                                                  Met Glu Thr Asp Thr
             cte ctg cta tgg qta ctg ctg ctc tgg gtt cca ggt tcc act ggt act
            Leu Leu Leu Trp Val. Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Thr
.265
            agt tgc gga aat atg ttt gtg gag ccg ggc gag cag tgt gac tgt ggc
Ser Cys Gly Asn Met Phe Val Glu Pro Gly Glu Gln Cys Asp Cys Gly
                                                     30
             tto etg gat gac tge gte gat ece tge tgt gat tet ttg ace tge eag
Phe Leu Asp Asp Cys Vel Asp Pro Cys Cys Asp Ser Leu Thr Cys Gln
40
             ctg agg cca ggt gca cag tgt gca tct gac gga ccc tgt tgt caa aat
Leu Arg Pro Gly Ala Gln Cys Ala Ser Asp Gly Pro Cys Cys Gln Asn
                                                                                              247
asi
             ige cag ctg ege ceg tet gge tgg cag tgt egt eet ace aga ggg gat
Cys Gln Leu Arg Pro Ser Gly Trp Gln Cys Arg Pro Thr Arg Gly Asp
                                                                                             295
             tgt gad ttg det gas ttd tgd des ggs gad age tod dag tgt ded det
Cys Asp Leu Pro Glu Phe Cys Pro Gly Asp Ser Ser Gln Cys Pro Pro
             gat gic ago cia ggg gat ggc gag ccc igc get ggc ggg caa gct gig
             Asp Val Ser Leu Gly Asp Gly Glu Pro Cys Ala Gly Gly Gln Ala Val
                           105
                                                   110
                                                                     115
```

	tyc	atg	cad	999	cgt	tgt	gec	toc	tat	gcc	cag	cag	tge	cag	tca	ctt	439
g.	Cys	Met	His 120	esa	Arg	Cys	Ala	Ser 125	Tyr	Ala	Gln	Gln	Cys 130	Gln	Ser	Leu	
*	tyg Trp	9ga 61y 135	ect Pre	gga Gly	gcc Ala	cag Gln	ecc Pro 140	get Ala	gcg Ala	cca Pro	ctt Leu	tgc Cys 145	ctc	cag Gln	aca Thr	gct Ala	487
10	ant Asn 150	act The	cgg Arg	gga	aat Asn	get Ala 155	Phe	ggg ggg	agc Ser	tgt Cys	999 999	cgc Arg	aac Asn	ecc Pro	agt Ser	ggc Gly 165	535
15	agt Ser	tat Tyr	gtg Val	tcc Ser	tgc Cys 170	acc Thr	Pro	aga Arg	gat Asp	gcc Ala 175	att Ile	tgt Cys	ggg Gly	cag Gln	ctc Leu 180	cag Gln	583
	tgc Cys	cag Gln	aca Thr	Gly 185	yrg	acc Thr	cag Gln	cct Pro	ctg Leu 190	ctg	ggc	tec Ser	atc	cgg Arg 195	gat Asp	cta Leu	631
20	Leu	tgg Trp	gag Glu 200	aca	ata Ile	gat Asp	gtg Val	aat Asn 205	GJA äää	act Thr	gag Glu	etg Leu	aac Asn 21.0	tgc Cys	agc Ser	tgg Trp	679
26	gtg Val	cac His 215	ctg Leu	gac Asp	ctg Leu	Gly	agt Ser 220	gat Asp	gtg Val	gcc Ala	cag Gln	ecc Pro 225	ctc	ctg Leu	act Thr	atg Leu	727
20	Pro 230	ggc Gly	Thr	gcc Ala	tgt. Cys	ggc Gly 235	Pro	Gly	ctg Leu	grg Val	tgt Cys 240	ata Ile	gac Asp	cat His	cga Arg	tgc Cys 345	775
30	cag Gln	egt Arg	gtg Val	gat Asp	ctc Leu 250	ctg Leu	ejà aaa	gca Ala	cag Gln	gaa Glu 255	tgt Cys	cga Arg	agc Ser	aaa Lys	tgc Cys 260	cat His	823
85	GJA Bās	cat His	ely ags	gtc Val 265	tgt Cys	gac Asp	agc Ser	aac Asn	agg Arg 270	cac His	tga Cys	tac Tyr	tgt Cys	gag Glu 275	gag Glu	ggc Gly	871
	tgg Trp	gca Ala	ecc Pro 280	Pro	gac Asp	tgc Cys	acc	act Thr 285	cag Gln	ste beu	aza Lys	gca Ala	acc Thr 290	agc Ser	tec Ser	aga Arg	919
40	tet Ser	tgt Cys 295	gac Asp	aaa Lys	act	cac His	aca Thr 300	tgc Cys	cca Pro	ccg Pro	tgc Cys	cca Pro 305	gca Ala	oct Pro	gaa Glu	gcc Ala	967
	gag Glu 310	ggc Gly	gcg Ala	ecg	tca Ser	gte Val 315	ttc Phe	cte Leu	Phe	eec Pro	eca Pro 320	aaa Lys	Pro	aag Lys	gac Asp	ace Thr 325	1015
45	Leu	atg Met	atc	tee Ser	cgg Arg 330	ace	ect Pro	gag Glu	gtc Val	aca Thr 335	tge Cys	gtg Val	gtg Val	gtg Val	gac Asp 340	gtg Val	1063
80	agc Ser	cac His	gaa Glu	gac Asp 345	ret	gag Glu	gtc Val	aag Lys	ttc Phe 350	aac Asn	tgg Trp	tac Tyr	gtg Val	gac Asp 355	Gly	gtg Val	1111
	gag Glu	gtg Val	cat His 360	aat Asn	gcc Ala	aag Lys	aca Thr	aag Lys 365	eeg Pro	egg årg	gag Glu	gag Glu	cag Gln 376	tac Tyr	aac Asn	agc Ser	1159
55	вeg	tac	cgt	gtg	gtc	agc	gtc	ete	acc	gtc	ctg	cac	cag	gac	tgg	ctg	1207

	Thx	Tyr 375	Arg	Val	Val	Ser	Val 380	Leu	Thr	Val	Leu	His 385	Gla	Asp	Trp	Leu	
5				gag Glu													1255
				aaa lys													1303
10	cag Glu	gtg Val	tac Tyr	acc Thr 425	ctg Leu	ecc	cca Pro	tcc Ser	cgg Arg 430	gag Glu	gag Glu	atg Met	acc Thr	aag Lys 435	aac Asn	cag Gln	1351
15				acc													1399
				gag Glu													1447
20	ect Pro 470	ccc	gtg Val	ctg	gac Asp	tee Ser 475	gac Asp	Gly	tee Ser	ttc Phe	ttc Phe 480	ctc	tat Tyr	agc Ser	aag Lys	ctc Leu 485	1495
25	acc	gt.g Val	gac Asp	rys	agc Ser 490	agg	tgg	cag Gln	cag Gln	999 Gly 495	aac Asn	gtc Val	ttc Phe	tca Ser	tgc Cys 500	tec Ser	1.543
				gag Glu 505													1591
ac				ggt			act	agag	ರಥಿತ (ccgc	cacc	gc g	gtgg	aget			1638
95	<21 <21 <21	3> D	RT rtif escr	icía ipti epti	on o			cial	Seq	uenc	e: f	usio	n.				
46	<40	0> 8															
	Met 1	Glu	Thr	Asp	Thr 5	Leu	Leu	Leu	Trp	Val 10	Leu	Leu	Leu	Trp	Val	Pro	
	GIÃ	Sex	The	Gly 20		Sex	Cys	Gly	Asn 25	Met	Phe	Val	Glu	Pro 30	Gly	Glu	
45	Gln	Cys	Asp 35		Gly	Phe	Leu	Asp 40		CAR	Val	qaA	Pro 45	cys	Cys	Asp	
	Ser	Leu	Thr		Glu	Leu	Arg 55	Pro		Ala	Gln	Cys 60		Ser	Asp	Gly	
	Pro 65	Cys		Gin	Asn	Cys 70	Gir		Arg	Pro	Ser 75		Trp	Gin	Cys	Arg 80	
5G			Arg	GLy	Asp 85	Cys		Leu	Pro	Glu 90	Phe	Cys	Pro	Gly	Asp	Ser	
	Ser	GIr	Cys	2rc	Pro		Val	Ser	Leu 105	Gly		Gly	Glu	Pro	Cys	Ala	
	Gly	GLy	Glr.	Ala		Cys	Met	His 120	Gly		Cys	Ala	Ser 125	Tyx		Gln	
ś.ii	Gly	Cys 130	Gla		Lev	Trp	Gly 135	Pro		Ala	Gln	Pro 140	Ala		Pro	Leu	

```
Cys Leu Gin Thr Ala Asn Thr Arg Gly Asn Ala Phe Gly Ser Cys Gly
          145
                             150
          Arg Asn Pro Ser Gly Ser Tyr Val Ser Cys Thr Pro Arg Asp Ala Ile
165 170
          Cys Gly Gln Leu Gln Cys Gln Thr Gly Arg Thr Gln Pro Leu Leu Gly
                                        185
          Ser Ile Arg Asp Leu Leu Trp Glu Thr Ile Asp Val Asm Gly Thr Glu
195 200 205
          Leu Asn Cys Ser Trp Val His Leu Asp Leu Gly Ser Asp Val Ala Gln
             210
                                  215
10
          Pro Leu Leu Thr Leu Pro Gly Thr Ala Cys Gly Pro Gly Leu Val Cys 225 230 230
          Ile Asp His Arg Cys Gin Arg Val Asp Leu Leu Gly Ala Gin Glu Cys
245 250 255
                                                                     255
          Arg Ser Lys Cys His Gly His Gly Val Cys Asp Ser Asm Arg His Cys
260 265 270
25
          Tyr Cys Glu Glu Gly Trp Ala Pro Pro Asp Cys Thr Thr Gln Leu Lys
                                     280
                                                             285
          Ala Thr Ser Ser Arg Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
290 295 300
          Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
                               310
                                                   325
20
          Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                          325
                                             330
          Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
340 345 350
          Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
355 360 365
          Glu Glm Tyr Asm Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
370 380
          His Gin Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
185 390 400
          Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                           405
                                               410
307
          Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
                      420
                                          425
          Met. Thr Lys Asn Glo Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
          Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
                                  455
                                                       460
          Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe 465 470 475
35
          Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
485 490 495
          Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
500 505 510
          Gin Lys Ser Leu Ser Leu Ser Pro Gly Lys
40
                   515
                                        520
          <210> 9
          <211> 1386
45
          <212> DNA
          <213> Artificial Sequence
          <220>
          <223> Description of Artificial Sequence: fusion
               polypeptide
          <220>
          <221> CDS
```

<400> 9 gtogaccess getggetage cace atg gag aca gad aca etc etg eta tgg

<222> (25)..(1365)

Met Glu Thr Asp Thr Leu Leu Leu Trp

gta etg etg etc teg gt cea ggt Val Leu Leu Leu Trp Val Pro Gly 10 teg agg gtg gat gaa gga gaa gag	Ser Thr Gly Thr Ser Cys Gly Asn 20 25
tog agg gtg gat gaa goa caa cac	
Ser Arg Val Asp Glu Gly Glu Gle	tgt gat cot ggc atc atg tat ctg 147 Cys Asp Pro Gly Ile Het Tyr Leu 35 40
asc asc use acc type type asc age	gac tgc acg ttg aag gaa ggt gtc 195
Asn Asn Asp Thr Cys Cys Asn Ser	Asp Cys Thr Leu Lys Glu Gly Val
45	50 55
cag tgc agt gac agg sac agt cct Gln Cys Ser Asp Arg Asn Ser Pro 60 65	tge tgt aaa aac tgt cag ttt gag 243 Cys Cys Lys Asn Cys Gln Phe Glu 70
act gcc cag aag aag tgc cag gag	gcg att aat gct act tgc aaa ggc 291
Thr Ala Cln Lys bys Cys Gln Glu	Ala Ile Asn Ala Thr Cys Lys Gly
75 80	85
gtg ten tan tge ana ggt aat age	agt gag tgc ccg cct cca gga aat 339
Val Ser Tyr Cys Thr Gly Asn Ser	Ser Glu Cys Pro Pro Pro Gly Asn
90 95	100 105
gct gaa gat gac act gtt tgc ttg	gat ctt ggc aeg tgt aag get ggg 187
Ala Glu Asp Asp Thr Val Cys Leu	Asp Leu Gly Lys Cys Lys Asp Gly
110	115 120
	gaa cag cag ctg gag tcc tgt gca 435 Glu Gln Gln Leu Glu Ser Cys Ala 136 135
tgt aat gaa act gac aac tcc tgc	aag gtg tgc tgc agg gac ett tcc 483
Cys Asn Glu Thr Asp Asn Ser Cys	Lys Val Cys Cys Arg Asp Leu Ser
140	180
ggc cgc tgt gtg ccc tat gtc gat	got gan cas eag sec the tht trg 531
Gly Arg Cys Val Pro Tyr Val Asp	Ala Glu Gin Lys Asn Leu Phe Leu
155 160	165
agg mam gga mag coc tgt mcm gta	gga ttt tgt gac atg aat ggc aaa 579
Arg Lys Gly Lys Pro Cys Thr Val	Gly Phe Cys Asp Met Asn Gly Lys
170	180 185
tgt gag aaa cga gta cag gat gta	att gaa cga ttt tgg gat ttc att 627
Cys Glu Lys Arg Val Gln Asp Val	Ile Glu Arg Phe Trp Asp Phe Ile
199	195 200
gac cag ctg agc atc aat act ttt	gga aag ttt tta gca gac aac aga 675
Asp Gln Lew Ser Ile Asn Thr Phe	Gly Lys Phe Leu Ala Asp Asn Arg
205	210 215
tet Egt gae aaa act cac aca tge	cca ccg tgc cca gca cct gaa gcc 723
Ser Cys Asp Lys Thr His Thr Cys	Pro Pro Cys Pro Ala Pro Glu Ala
220 225	230
gay ggc gcg ccg tca gtc ttc ctc Glu Gly Ala Pro Ser Val Phe Leu 235 240	ttc occ cca ama occ ama gac acc 771 Phe Pro Pro Lys Pro Lys Asp Thr 245
ctc atg atc tcc cgg acc cct gag	gtc aca tgc gtg gtg gtg gac gtg 819
Leu Met lle Ser Arg Thr Pro Glu	Val Thr Cys Val Val Val Asp Val
55 250 255	260 265

	agc Ser	cac His	gaa Glu	gae Asp	eet Pro 270	gag Glu	gte Val	aag Lys	tte Phe	aac Asn 275	tgg Trp	tac Tyr	gtg Val	gac Asp	ggc Gly 280	gtg Val	867
5	gag Glu	gtg Val	cat His	aat Asn 285	gcc Ala	aag Lys	aca Thr	aag Lys	ecg Pro 290	cgg Arg	gag Glu	gag Glu	cag Gln	tac Tyr 295	aac Ass	ago Ser	915
1G				gtg Val													963
	aat Asn	ggc Gly 315	aag Lys	gag Glu	tac Tyr	aag Lys	tgc Cys 320	aag Lys	gtc Val	tcc Ser	aac Asn	aaa Lys 325	gec Ala	ctc Leu	cca Pro	gcc Ala	1011
15	ecc 330	atc	gag Glu	aaa Lys	ace Thr	atc 11e 335	ser	aaa Lys	gcc Ala	aaa Lys	999 Gly 340	cag Gln	ecc Pro	ega Arg	gaa Glu	cca Pro 345	1059
20	cag Gln	gtg Val	tac Tyr	acc	ctg Leu 350	Pro	cca Pro	tcc Ser	egg Arg	gat Asp 355	gag Glu	ctg	acc Thr	aag Lys	aac Asn 360	Gln	1107
				acc Thr 365													1155
20				gag Glu													1203
30				ctg Leu													1251
				aag Lys													1299
36	gtg Val	atg Met	Cat	gag Glu	get Ala 430	ctg Leu	His	aac Asn	cac His	Tyr 435	acg	cag Gln	aag Lys	agc Ser	Ctc Les 440	tcc Ser	1347
40	ctg Leu	tct Ser	eeg Pro	99t 61y 445	aaa Lys	tga	act	agag	cgg (cede	tace	ga t					1386
	<21	0> 1 1> 4 2> P	46														
45	<21	3> A 3> D	rtif escr	ícia iprí epti	on o			cial	Seq	ienc	e: f:	usio	n				
		0> 1					-										
50	1			Asp	5					10					15		
				20 Pro					. 25					30			
			35					40					45				
55		50	- 4				55					60	.,,	9			

```
Fro Cys Cys Lys Asn Cys Gln Phe Glu Thr Ala Gln Lys Lys Cys Gln
65 70 75 80
Glu Ala Ile Asn Ala Thr Cys Lys Gly Val Ser Tyr Cys Thr Gly Asn
                 85
                                      90
                                                           95
Ser Ser Glu Cys Pro Pro Pro Gly Asn Ala Glu Asp Asp Thr Val Cys
                                 105
                                                      110
Lem Asp Lem Gly Lys Cys Lys Asp Gly Lys Cys Ile Pro Phe Cys Glu
115 120 125
Arg Glu Gln Gln Leu Glu Ser Cys Ala Cys Asn Glu Thr Asp Asn Ser
   130
                       135
                                           140
Cys Lys Val Cys Cys Arg Asp Leu Ser Gly Arg Cys Val Pro Tyr Val
145 150 155 160
                                         155
Asp Ala Glu Gln Lys Asn Leu Phe Leu Arg Lys Gly Lys Pro Cys Thr
165 170 175
Val Gly Phe Cys Asp Met Asn Gly Lys Cys Glu Lys Arg Val Gln Asp
Val Ile Glu Arg Phe Trp Asp Phe Ile Asp Gln Leu Ser Ile Asn Thr
       195
                             200
                                                  205
Phe Cly Lys Phe Leu Ala Asp Asn Arg Ser Cys Asp Lys Thr His Thr
  210
                        215
Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe
225 230 235
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270
Lys Fhe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
                                              300
Leu Thr Val Leu Ris Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                   310
                                        315
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                 325
                                    330
                                                          335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340
                                 349
Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val 355
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly 370 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Vel Leu Asp Ser Asp
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405
                                    410
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
                                425
            420
                                                      430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                              440
```

```
<210> 11
<211> 1653
<212> DNA
<213> Artificial Sequence
```

15

20

25

30

38

40

AK

<220>

<223> Description of Artificial Sequence: fusion polypeptide

<220> <221> CDS <222> (25)..(1632)

<400> 11 gtogaccosa getggetage cace atg gag aca gae aca etc etg eta tgg 5:

Met Glu Tor Asp Thr Leu Leu Leu Trp

5	gta Val 10	ctg Leu	ctg Leu	ctc	tgg Trp	gtt Val 15	eca Pro	ggt Gly	tcc \$er	act. Thr	ggt Gly 20	act Thr	agt Ser	tgt Cys	61 y	aat Asn 25	99
10	Leu	gre Val	gtt Val	gaa Glu	gaa Glu 30	GJA aaa	gag Glu	gaa Glu	tgt Cys	gac Asp 35	tgt Cys	gga Gly	acc Thr	ata Ile	egg Arg 40	cag Gln	147
	tgt Cys	gca Ala	Lys	gat Asp 45	ecc ecc	tgt Cys	tgt Cys	ctg Leu	tta Leu 50	aac Asn	tgt Cys	act Thr	cta Leu	cat His 55	ect Pro	Gly ggg	195
15	get Als	gct Ala	tgt Cys 60	gct Ala	ttt Phe	Gly gga	eta Ile	tgt Cys 65	tgc Cys	rys	gac Asp	tgc Cys	aaa Lys 70	ttt Phe	ctg Leu	cca Pro	243
20	tca Ser	gga Gly 75	act Thr	tta Leu	tgt Cys	aga Arg	caa Gln 80	caa Gln	gtt Val	ggt Gly	gaa Glu	tgt Cys 85	gac Asp	ctt Leu	eca Pro	gag Glu	291
	tgg Trp 90	tgc Cys	aet Asn	217 233	aca Thr	Ser 95	cat His	caa Gln	tgc Cys	cca Pro	gat Asp 100	gat Asp	gtg Vai	tat Tyr	gtg Val	cag Gln 105	339
25	gac Asp	G1Y G9G	atc Ile	tee Ser	tgt Cys 110	aat Asn	gtg Val	aat	gcc Ala	ttc Phe 115	tgc Cys	tat Tyr	gaa Glu	aag Lys	acg Thr 120	tgt Cys	387
30	aat Asn	aac Asn	cat His	gat Asp 125	ata Ile	caa Gln	Cys Cys	aaa Lys	gag Glu 130	att Ile	t.cc Phe	Gly	caa Gln	gat Asp 135	gca Ala	agg Arg	435
(10)	agt. Ser	gca Ala	tct Ser 140	cag Gln	agt Ser	tge Cys	tac Tyr	caa Gln 145	gaa Glu	atc	aac Asn	Thr	caa Gln 150	gga Gly	aac Asn	egt Arg	483
35	Phe	ggt Gly 155	Ris	tgt Cys	ggt Gly	att Ile	gta Val 160	Gly	aca Thr	aca Thr	tat Tyr	gta Val 165	aaa Lys	tgt Cys	tgg Trp	acc Thr	531
	Pro 170	gat Asp	atc	atg Met	tgt Cys	999 Gly 175	agg Arg	gtt Val	cag Gln	tgt Cys	gaa Glu 180	aat Asn	gtg Val	Gly	gta Val	att Ile 185	579
40	ecc Pro	aat Asn	ctg Leu	ata Ile	gag Glu 190	cat His	tot Ser	aca Thr	gtg Val	cag Gln 195	cag Gln	ttt Phe	eac Ris	Leu Leu	aat Asn 200	gac	627
45	Thr	act	tgc Cys	tgg Trp 205	Gly	act Thr	gat Asp	tat Tyr	cat His 210	tta Leu	g1A aaa	atg Met	gct Ala	ata Ile 215	cct Pro	gat Asp	675
	att Ile	gg: Gly	gag Glu 220	gtg Val	aaa Lys	gat	GJ¥ ggc	aca Thr 225	gta Val	tgt. Cys	ggt Gly	cca Pro	gaa Glu 230	aag Lys	atc Ile	tgc Cys	723
50	atc Ile	cgt Arg 235	aag Lys	aag Lys	tgt Cys	gcc	agt Ser 240	atg Met	gtt Val	cat His	ctg Leu	ser 245	caa Gln	gcc Ala	tgt Cys	cag Gln	771
56	oct Pro 250	aag Lys	acc	egc Cys	aac Asn	atg Met 255	agg Arg	gga Gly	atc	tgc Cys	aac Asn 260	aac Asn	aaa Lys	caa Gln	cac His	tgt Cys 265	819

	car Ris	tgc Cys	aac Asn	cat His	gaa G1u 270	tgg Trp	gca Ala	Pro	cca Pro	tac Tyr 275	Cys	aag Lys	gac	aaa Lys	ggc Gly 280	tat Tyr	867
5	gga Gly	ggt Gly	agt Ser	gct Ala 285	gat Asp	agt Ser	Gly	eca Pro	oct Pro 290	cct Pro	aag Lys	aac Asn	aac Asn	atg Met 295	gas Glu	gga Gly	915
10	tta Leu	aat Asn	gtg Val 300	atg Met	G13 ggs	aag Lys	ttg Leu	egt Arg 305	gga Gly	tct Ser	tgt Cys	gac Asp	aaa Lys 310	act	cac Rís	aca Thr	963
	tgc Cys	cca Pro 315	rcy Pro	tgc Cys	cca Pro	gca Ala	Pro 320	gaa Glu	gcc Ala	gag Glu	GJ X BBc	gcg Ala 325	ecg	tca Ser	gtc Val	ctc Phe	1011
16	Leu 330	ttc Phe	coc Pro	cca Pro	aaa Lys	Pro 335	aag Lys	gac Asp	acc Thr	etc Leu	atg Met 340	atc Ile	tcc Ser	egg	acc	cct Pro 345	1059
20	gag Glu	gtc Val	aca Thr	Cys Cys	gtg Val 350	gtg Val	gtg Val	gac Asp	gtg Val	age Ser 355	cac Ris	gaa Glu	gac Asp	ect Pro	gaş Glu 360	gte Val	1107
	aag Lys	ttc Phe	aac Asn	tgg Trp 365	tac Tyr	gtg Val	yab	ggc Gly	gtg Val 370	gag Glu	gtg Val	cat His	aat Asn	gec Ala 375	aag Lys	aca Thr	1255
25	aag Lys	Pro	cgg Arg 380	gag Glu	gag Glu	cag Gln	tac Tyr	asc Asn 385	agc Ser	acg Thr	tac Tyr	cgg Arg	gtg Val 390	gtc Val	age Ser	gtc Val	1203
367	Leu	Thr 395	gtc Val	ctg Leu	cac His	Cag Gln	gac Asp 400	tgg Trp	ctg Leu	aat Asn	Gly	aag Lys 405	gag Glu	tac	aaq Lys	Cys	1251
	Lys 410	gtc Val	tee Ser	aac Asn	aaa Lys	gec Ala 415	ctc Leu	cca Pro	gcc Ala	ecc Pro	atc Ile 420	gag Glu	aaa Lys	acc Thr	atc Ile	tcc Ser 425	1299
36	Lys	YIB	Lys	GIY	63n	Pro	Arg	Glu	Pro	cag Gln 435	Val	Tyr	Thr	Lou	Pro 440	Pro	1347
40	tec Ser	egg Arg	gat Asp	949 Glu 445	ctg Leu	Thr	aag Lys	aac Asn	cag Gln 450	gtc Val	agc Ser	ctg	ace Thr	tgc Cys 455	ctg Leu	gte Val	1395
	nan Lys	ggc Gly	the 160	tat Tyr	Pro	agc Ser	gac Asp	atc Tle 465	gcc Ala	gtg Val	gag Glu	tgg Trp	gag Glu 470	agc Ser	aat Asn	G1y	1443
45	cag Gln	eeg Pro 475	gag Glu	aac Asn	aac	tac Tyr	aag Lys 480	acc Thr	acg Thr	ect. Pro	ece Pro	gtg Val 485	ctg Leu	gac Asp	tec Ser	gad Asp	1491
80	ggc Gly 490	Ser	tre Phe	tte	Leu	tac Tyr 495	agc Ser	aag Lys	ctc Leu	acc	gtg Val 500	gac Asp	aag Lys	agc Ser	agg Arg	tgg Trp 505	1539
	cag Gln	cag Gln	999 Gly	aac Asn	9tc Val 510	ttc Phe	tca Ser	tgc Cys	tec Ser	gtg Val 515	atg Met	cat His	gaç Glu	get Ala	etg Leu 520	cac His	1587
56	aac	cac	tac	acg	cag	aag	age	ara	tec	ctg	tet	cag	ggt	aaa	tga		1632

1653

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 525 530 530

actagagogg cogotacaga t 33 <210> 12 <211> 535 <212> PRT <213> Artificial Sequence 10 <223> Description of Artificial Sequence: fusion polypeptide <400> 12 Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro 18 Gly Ser Thr Gly Thr Ser Cys Gly Asn Leu Val Val Glu Glu Gly Glu 20 25 30 Glu Cys Asp Cys Gly Thr Ile Arg Gln Cys Ala Lys Asp Pro Cys Cys 35 40 45 Leu Leu Asn Cys Thr Leu His Pro Gly Ala Ala Cys Ala Phe Gly Ile 50 S5 60 20 Cys Cys Lys Asp Cys Lys Phe Leu Pro Ser Gly Thr Leu Cys Arg Glm Gin Val Gly Glu Cys Asp Leu Pro Glu Trp Cys Asn Gly Thr Ser His 85 90 95 Gln Cys Pro Asp Asp Val Tyr Val Gln Asp Gly Ile Ser Cys Asn Val 100 105 Asn Ala Phe Cys Tyr Glu Lys Thr Cys Asn Asn His Asp Ile Gln Cys 25 Lys Glu The Phe Gly Gln Asp Ala Arg Ser Ale Ser Gln Ser Cys Tyr 130 135 140 Gin Glu Ile Asn Thr Gin Gly Asn Arg Phe Gly His Cys Gly Ile Val 150 Gly Thr Thr Tyr Val Lys Cys Trp Thr Pro Asp Ile Met Cys Gly Arg 165 170 Val Gln Cys Glu Asn Val Gly Val Ile Pro Asn Leu Ile Glu His Ser 180 185 190 Thr Val Gin Gin Phe His Leu Asn Asp Thr Thr Cys Trp Gly Thr Asp 205 28 Tyr His Leu Gly Met Ala Ile Pro Asp Ile Gly Glu Val Lys Asp Gly 210 215 220 Thr Val Cys Gly Pro Glu Lys Ile Cys Ile Arg Lys Lys Cys Ala Ser 225 230 235 Met Val His Leu Ser Gln Ala Cys Gln Pro Lys Thr Cys Asn Met Arg 250 40 Gly Ile Cys Asn Asn Lys Gln His Cys His Cys Asn His Glu Trp Ala 260 265 270 260 Pro Pro Tyr Cys Lys Asp Lys Gly Tyr Gly Gly Ser Ala Asp Ser Gly 275 280 285 Pro Pro Pro Lys Asm Asm Met Glu Gly Leu Asm Val Met Gly Lys Leu 240 295 300 295 300 Arg Gly Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro 305 310 315 320 45 Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys 325 330 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Vai Thr Cys Val Val Val 340 345 Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp 360 365 Sly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 375 380 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp 396 395 Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu

410

405

	Pro A	la Pro	11e 420	Glu	Lys	Thr	Ile	Ser 425	Lys	Ala	Lys	Gly	Gln 430	Pro	Arg	
	Glu P	ro Gla 435		Tyr	Thr	Leu	Pro 440		Ser	Arg	Asp	Glu 445		Thr	Lys	
5		ln Val	Ser	Leu	Thr	Cys 455		Val	Lys	Gl¥	Phe 460		Pro	Ser	Asp	
	Ile Al 465	la Val	Glu	Trp	Glu 470		Asn	Gly	Gln	Pro 475		Asn	Asn	Tyr	Lys 480	
		hr Pro	Pro	Уа1 485		Asp	Ser	Asp	Gly 490		Phe	Phe	Leu			
112	Lys L	eu Thr	Val 500		Lys	ser	Arg	Trp		Gln	Gly	Asn		195 Phe	Ser	
	Cys S	er Val		His	Glu	Ala		50S His	Asn	His	Tyr		510 Gln	Lys	Ser	
		er Leu	Ser	Pro	Gly		520					525				
15	5.	30				535										
	<210> <211> <212> <213>	1617	icia.	l Sec	quenc	ce ce										
3202	<220>															
	<223>	Descr			E Ari	cifí	cial	Seg	uenc	e: fu	isio	ī				
	<220>															
25	<221>	(25).	. (15	96)												
	<400>	13 cccaa	getg	gata	ge e	ace i	det i	jag i 31u '	aca :	gac a	fhr 1	etc «	ctg : Leu l	oba : Geu '	rgg rgg	51
30							1				5					
	gta c Val L 10	tg ctg eu Leu	Leu	Trp	yal Val 15	Pro	ggt G1y	Ser	Thr	Gly 20	Thr	agt Ser	tgt Cys	g J A a a a	aat Asn 25	99
36	ggt g		CYNE	aga	gaa	an.										
30	Gly V	tg gtt al Vel	Glu	Arg 30	Glu	Glu	Gln	tgt Cys	gac Asp 35	tgt Cys	gga Gly	tee Ser	Val	Gln 40	Gln	147
30	Gly V	tg gtt al Vel ea caa lu Gln	Glu gac Asp	30 gcc	Glu	Glu	Gin	Cys ttg Leu	Asp 35 aac	Cys	Gly	Ser	val agg Arg	Gln 40	Gln	147
30 40	tgt g Cys G	al Vel ee caa lu Gln	gac Asp 45	Arg 30 gcc Ala	tgt Cys	glu tgt Cys	Gln ctg Leu	ttg Leu 50	aac Asn	Cys tgc Cys	Gly act Thr	Ser cta Leu	agg Arg 55	Gln 40 cct Pro	gly ggg	
	tgt g Cys G	al Vel	gac Asp 45	Arg 30 gcc Ala ttt	tgt Cys	tgt Cys	Gln ctg Leu	ttg Leu 50	Asp 35 aac Asn aaa	Cys tgc Cys gac	act Thr	Ser cta Leu	agg Arg 55	Gln 40 cct Pro	gln ggg Gly	
	Gly V tgt g Cys G gct g Ala A tca g	al Vel aa caa lu Gin cc tgt la Cys	gac sap 45 45 get Ala	Arg 30 gcc Ala trt Phe	tgt Cys egg Gly	tgt Cys ctt Leu	Gin ctg Leu tgt Cys 65	ttg Leu 50 tgc Cys	Asp 35 aac Asn aaa Lys	tgc Cys gac Asp	Gly act Thr tgc Cys	cta Leu sag Lys 70	agg Arg 55 ttc Phe	Gin 40 cct Pro atg Net	Gin ggg Gly cca Pro	195
40	Gly V tgt g Cys G gct g Als A tca g Ser G	ea cae lu Gln cc tgt le Cys 60	gac Asp 45 gct Ala	Arg 30 gec Ala trt Phe tgt Cys	tgt Cys egg Gly aga Arg	tgt Cys ctt Leu caa Gln 80	ctg Leu tgt Cys 65 gag Glu	ttg Len 50 tgc Cys gtc Val	ase Asn asa Lys ast Asn	tge Cys gac Asp gaa Glu	Gly act Thr tgc Cys tgc Cys 85	cta Leu aag Lys 70 gac Asp	agg Arg 55 ttc Phe ctt Leu tat	Gin 40 cct Pro atg Met cca Pro	cad daw cra bro cra daw cra ada din	195 243
40	tgt g tgt g Cys G gct g Ala A tea g Ser G tgg t Trp C gar g	al Val ea caa lu Gln cc tgt la Cys 60 gg gaa 17 Glu 75	gac Asp 45 get Ala ctc Leu	Arg 30 gcc Ala ttt Phe tgt Cys aca Thr	tgt Cys egg Gly aga Arg tct Sex 95	caa Gln cat Ris	cts Leu tgt Cys 65 gag Gle cag Gle	Cys ttg Len 50 tgc Cys gtr Val tgt Cys	ase ase ase Lys ast ase ase ase ase ase ase ase ase ase ase	Cys tgc Cys gac Asp gaa Glu gaa Clu 100	Gly act Thr tgc Cys tgc Cys gat Asp	cta Leu aag Lys 70 gac Asp aga Arg	agg Arg 55 ttc Phe ctt Leu tat Tyr	Gin 40 cct Pro atg Met cca Pro gtg Val	gas Glu cag Gln 105	195 243 291

								EF	1 80	3 81	0 A1						
	Asn	Asn	Ris	Asp 125	Gln	His	Cys	Arg	Glu 130	Ile	Phe	Gly	Lys	Asp 135	Ala	Lys	
ş	agt Ser	gca Ala	tct Ser 140	cag Gln	áat Asn	Lğc Cys	tet Tyr	aaa Lys 145	gaa Glu	atc Ile	aac Asn	tct Ser	cag Gin 150	gga Gly	aac Asn	egt Arg	483
10	ttt Phe	99t 61y 155	cac His	tgt Cys	ggt Gly	ata Ile	aat Asn 160	ggc Gly	aca Thr	aca Thr	tac Tyr	cta Leu 165	aaa Lys	tgt Cys	cat	atc Ile	531
	Ser 170	gat	gtc Val	Phe	tgt Cys	ggg Gly 175	aga	gtt Val	caa Gln	tgt Cys	gag Glu 180	aat Asn	gtg Val	aga Arg	gac Asp	att Ile 185	579
15	ect Pro	ctt Leu	ctc Leu	caa Gln	gat Asp 190	cat His	ttt Phe	act Thr	ttg Leu	cag Gln 195	cac His	act	cat His	atc	aat Asn 200	ggt Gly	627
200	gtc Val			Trp 205													675
	att 11e	ggt Cly	gaa Glu 220	gtg Val	rys	gat Asp	Gly	act Thr 225	gtg Val	tgt Cys	ggc Gly	Pro	gga Gly 230	aag Lys	atc Ile	tgc Cys	723
25	ate Ile	Cat His 235	LYS	aag Lys	tgt Cys	gtc Val	agt Ser 240	Leu	tet Ser	gtc Val	t tg Leu	Ser 245	cat His	gte Val	Cys	ctt Leu	771
30				tgc Cys													819
	cac His	tgt Cys	qgc Gly	tat Tyr	ggg Gly 270	tgg Trp	tcc Ser	Pro	Pro	Tyr 275	tgc Cys	eag Gln	cac Hia	aga Arg	Gly 280	tat Tyr	867
35	Gly	Gly	Ser	Ile 285	Asp	Ser	Gly	Pro	Ala 290	Ser	Ala	Lys	Arg	Ser 295	Cys	qsā	915
40	Lys	Thr	His 300	aca Thr	Cys	Pro	Pro	Cys 305	Pro	Ala	Pro	Glu	Ala 310	Glu	GJĀ	Ala	963
	Pro	Ser 315	Val	Phe	Leu	Phe	320	Pro	Lys	Pro	Lys	Asp 325	Thr	Leu	Met	Ile	103.1
46	330	Arg	Thx	Pro	Glu	Val 335	Thr	Cys	Val	Val	Val 340	Asp	Val	Ser	His	Glu 345	1059
50	Asp	Pro	GLu	gtc Val	150	Phe	Asn	Trp	Tyr	7a1 355	Asp	GJA	Val	Glu	360	Ris	1107
	Asn	Ala	Lys	Thr 365	Lys	Pro	årg	Glu	Glu 370	Gin	Tyr	Asn	Ser	Thr 375	Tyr	Arg	1155
55	gtg Val	gte Val	ser 380	Val	Leu	Thr	gtc Val	Leu 385	His	Gln	gac	tgg Trp	ctg Leu 390	aat Asn	gly	aag Lys	1203

	gag ta Glu Ty 39	r Lys														1251
5	aaa ac Lys Th 410															1299
10	acc ct Thr Le															3.347
	acc tg Thr Cy								Ser							1395
15	gag ag Glu Se		Gly													1443
20	otg ga Leu As 47	p Ser														1491
	aag ag Lys St 490	c agg	tgg Trp	cag Gln	cag Gln 495	gg9 Gly	aac Asn	gtc Val	ttc Phe	tca Ser 500	tgc Cys	tec	gtg Val	atg Met	cat His 505	1539
26	gag go Glu Al															1587
sic	ggt as		act	egag	cgg =	cege	caca	ga t								1617
85	<210> <211> <212> <213> <223>	523 PRT Artif	ipti	022 0			cial	Seg	uence	e: É	usio	n.				
	<400> Met G		. Amm	min en	Yen	rom	T als	Abres	trait	*	* ***	T	Maria	175.3	n.c.	
40	Gly S			S					10				_	15		4
***	Gln C				Ser	Val			Cys	Glu	Gln		30 Ala	Cys	Cys	
	Leu L	35 eu Ass 50		Thr	Leu	Arg 55	40 Pro		Ala	Ala	Cys 60	Ala	Phe	Gly	Leu	
45	Cys C		Asp	Cys	Lys		Met	Pro	Ser	Gly 75		Lou	Cys	Arg	GIn 80	
	Glu V	al Asr	Glu	Cys	Asp	Leu	Pro	Glu	Trp 90		Asn	Gly	Thr	Ser 95		
	Gln C	ys Pro	100	Asp		Tyr	Val	Gln 105		Cly	Ile	Pro	Cys 110		Asp	
50	Ser A	la Tys 115		Tyr	Oln	Lys	Arg	Cys	Asn	Asn	Hís	Asp 125		His	Cys	
		30				135					140					
	Lys G 145				150					2.55					160	
58	Gly T	ar Th	. AAz	165	Lys	Cys	His	Tle	Ser 170	Asp	Val	Phe	Cys	Gly 175		

Val Gin Cys Glu Asn Vel Arg Asp Ile Pro Leu Leu Gln Asp His Phe 180 185 Thr Leu Gla His Thr His Ile Asn Gly Val Thr Cys Trp Gly Ile Asp 195 200 205 Tyr His Leu Arg Met Asn Ile Ser Asp Ile Gly Glu Val Lys Asp Gly 210 215 220 Thr Val Cys Gly Pro Gly Lys Ile Cys Ile His Lys Lys Cys Val Ser 225 230 235 Leu Ser Val Leu Ser His Val Cys Leu Pro Glu Thr Cys Asn Met Lys 245 250 10 Cly lle Cys Asn Asn Lys His His Cys His Cys Gly Tyr Gly Trp Ser 260 265 270 Pro Pro Tyr Cys Gla His Arg Gly Tyr Gly Gly Ser Ile Asp Ser Gly 280 Pro Ala Ser Ala Lys Arg Ser Cys Asp Lys Thr Ris Thr Cys Pro Pro 290 295 300 15 Cys Pro Ala Pro Glu Ala Clu Gly Ala Pro Ser Val Phe Leu Phe Pro 310 315 Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr 325 330 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn 345 350 20 Trp Tyr Val Asp Gly Val Glu Val His Asm Ala Lys Thr Lys Pro Arg 355 360 365 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val 370 375 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser 385 390 395 390 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys 26 405 410 415 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp 420 425 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe 435 440 445 30 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu 450 455 460 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe 470 475 Fhe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gly 485 490 495 38 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr 500 505 Thr Gln bys Ser Leu Ser Leu Ser Pro Gly bys <210> 15 <211> 1674 <212> DNA <213> Artificial Sequence <223> Description of Artificial Sequence: fusion polypeptide <220> <221> CDS <222> (25)..(1653) 300 <400> 35 gtegacceaa getggetage cace atg gag aca gae aca ete etg eta tgg 53 Met Glu Thr Asp Thr Leu Leu Leu Trp 55 gta ctg ctg ctc tgg gtt cca ggt tcc act ggt act agt tgt ggc aat

	Val. 10	Leu	Leu	Leu	Trp	Val 15	Pro	GIÀ	Ser	Thr	Gly . 20	Thr	Ser	Cys	Gly	Asn 25	
5	61% 88c	ttc Phe	att	gaa Glu	act Thr 30	gga Gly	gag Slu	gag Glu	tgt Cys	gat Asp 35	tgt Cys	gga Gly	acc Thr	Pro	gec Ala 40	gaa Glu	147
10	tgt Cys	grc Val	ctt Leu	gaa Glu 45	GJA 339	gca Ala	gag Glu	tgt Cys	tgt Cys S0	aag Lys	aaa Lys	tgc Cys	acc Thr	teg Leu 55	act Thr	caa Gln	195
	gac Asp	tot Ser	caa Gln 60	tgc Cys	agt Ser	gac Asp	ggt Gly	ctt Leu 65	tge Cys	tgt Cys	aas Lys	aag Lys	tgc Cys 70	aeg Lys	trt Phe	cag Gln	243
18	ect Pro	atg Mat 75	ggc Gly	act Thr	gtg Val	tgc Cys	cga Arg 80	gaz Glu	gca Ala	gta Val	aat Ass	gat Asp 85	tgt Cys	gat Asp	atr Lie	egt Arg	291
207	gaa Glu 90	acg Thr	tgc Cys	tca Ser	gga Gly	aat Asn 95	tca Ser	agc Ser	cag Gln	tgt Cys	gec Ala 100	ect Pro	aat Asn	att 11e	cat His	aaa Lys 205	339
	atg Met	gat. Asp	G17 G39	tat Tyr	Ser 110	Cys	gat Asp	Gly	gtt Val	cag Gln 115	gga Gly	att	tgc Cys	ttt Phe	gga. Gly 120	gga Gly	387
28				acc Thr 125													435
	gtg Val	Thr	gce Ala 140	tca Ser	gac Asp	aaa Lys	tat	tgc Cys 145	tat Tyr	gag Glu	aaa Lys	ctg Leu	aat Asn 150	att Ile	gaa Glu	eja aaa	483
30	acg	gag Glu 155	aag Lys	G17 GGC	aac Asn	tgt Cys	999 61y 160	aca Lys	gac	aaa Lys	gac Asp	aca Thr 1.65	tgg Trp	ata Ile	cag Gln	tgc Cys	531
36	Asn 170	Lys	Arg	gat	gtg Val	Leu 175	tgt Cys	ggt Gly	tac	ctt Leu	ttg Leu 180	tgt Cys	acc	aat Asn	att	ggc Gly 185	579
	aat	atc	Pro	agg	Leu 190	Gly	gaa Glu	ctc Leu	gat. Anp	ggt Gly 195	gaa Glu	atc	aca Thr	tet Ser	act Thr 200	tra Leu	627
40	gtt Val	gtg Val	cag Gin	Gin 205	Gly	aga Arg	aca Thr	rta Leu	aac Asn 210	tgc Cys	agt Ser	Gly Gly	ejà ĉaa	cat Nis 215	gtt Val	aag Lys	675
45	ctt Leu	gaa Glu	gaa Glu 220	gat	gta Val	gat	Leu	990 Gly 225	tat Tyr	gtg Val	gaa Glu	gat Asp	ggg Gly 230	aca Thr	Pro	tgt Cys	723
	ggt	Pro 235	Gln	atg Met	Met	tgc Cys	tta Leu 240	gaa Glu	cac	agg Arg	tgt Cys	Ctt Leu 245	Pro	gtg Val	gct Ala	tct Ser	771
SG	ttc Phe 250	Asn	ttt Phe	agt	act	tgc Cys 255	t.t.g Leu	agc Ser	agt Ser	aaa Lys	gaa Glu 260	ggc Gly	act Thr	att	tgc Cys	tca Ser 265	819
55	gga Gly	Asn	gga Gly	gtt Val	tgc Cys 270	Ser	aat Asn	gag Glu	ctg Leu	aag Lys 275	tgt Cys	gtg Val	tgt Cys	aac Asn	aga Arg 280	cac His	867

	tgg Trp	ata Ile	ggt Gly	tet Ser 285	gat Asp	cys Cys	aac Asn	act Thr	tac Tyr 290	ttc Phe	cet Pro	cac His	aat Asn	gat Asp 295	gat Asp	gca Ala	915
5										ggt Gly							963
10										ccg							1011
	gag Glu 330	Gly ggc	gcg Ala	reg	tca Ser	gte Val 335	ttc Phe	Leu	ttc Phe	ecc Pro	cca Pro 340	aaa Lys	ece Pro	aag Lys	gac Asp	acc Thr 345	1059
15	cto Leu	atg Met	atc Ile	tec Ser	egg Arg 350	acc	cct Pro	gag Glu	gte Val	aca Thr 355	tge Cys	gtg Val	gtg Val	gtg Val	gac Asp 360	gtg Val	1107
30	agc Ser	cac Ris	gaa Glu	gac Asp 365	cct	gag Glu	gtc Val	aag Lys	ttc Phe 370	aac Asn	tgg Trp	tac Tyr	gtg Val	gac Asp 375	Gly	gtg Val	1.155
	gag Glu	gtg Val	cat His 380	aet Asn	gcc Ala	aag Lys	Thr	aag Lys 385	ccg Pro	Arg	gag Glu	gag Glu	Gln 390	tac Tyr	aac Asn	agc Ser	1203
25	acg Thr	tac Tyr 395	Arg	gtg Val	gtc Val	age Ser	gtc Val 400	etc Leu	acc	gtc Val	ctg Leu	cac His 405	cag Gln	gac Asp	tgg Trp	ctg Leu	1251
30	aat Asn 410	Gly	aag Lys	gag Glu	tac Tyr	aag Lys 415	tgc Cys	aag Lys	gtc Val	ser	aac Asn 420	aaa Lys	gcc Ala	ete Leu	eca	gcc Ala 425	1299
										aaa Lys 435							1347
35	Cag Gln	gtg Val	tac Tyr	Thr 445	ctg Leu	Pro	cca Pro	tec Ser	cgg Arg 450	gat Asp	gag Glu	ctg	acc Thr	aag Lys 455	aac Asn	cag Gln	1395
40										ttc Phe							1443
										gag Glu							1491
45	Pro 490	Pro	gtg Val	ctg	gac	Sex 495	gac Asp	ggc	Ser	ttc Phe	Phe 500	Leu	tac Tyr	agc Ser	aag Lys	ctc Leu 505	1539
80										999 61y 515							1587
	gtg Val	atg Met	cat	gag Glu 525	get	ctg Leu	cac His	eac Asn	cac His 530	tac	acg Thr	cag Gln	aag Lys	agc Ser 535	ctc	tec Ser	1635
58	ctg	tet	ccg	ggt	aaa	tge	act	agag	ogg ·	cege	tacas	ga t					1674

Leu Ser Pro Gly Lys 540

<210> 16

15

20

25

30

35

40

88

<211> 542

<212> PRT <213> Artificial Sequence

<223> Description of Artificial Sequence: fusion

polypeptide

<400> 16 Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Thr Ser Cys Gly Asn Gly Phe Ile Glu Thr Gly Glu Glu Cys Amp Cys Gly Thr Pro Ala Glu Cys Val Leu Glu Gly Ala Glu 35 48 Cys Cys Lys Lys Cys Thr Leu Thr Gln Asp Ser Gln Cys Ser Asp Gly 55 Leu Cys Cys Lys Lys Cys Lys Phe Gln Pro Met Gly Thr Val Cys Arg 55 70 75 80 Glu Ala Val Asn Asp Cys Asp Tie Arg Glu Thr Cys Ser Gly Asn Ser 85 90 95 Ser Gln Cys Ala Pro Asn Ile His Lys Met Asp Gly Tyr Ser Cys Asp 100 105 110 Gly Val Gln Gly Ile Cys Phe Gly Gly Arg Cys Lys Thr Arg Asp Arg Gin Cys bys Tyr Ile Trp Gly Cln bys Val Thr Ala Ser Asp bys Tyr 130 140 Cys Tyr Glu Lys Leu Asm Ile Glu Gly Thr Glu Lys Gly Asm Cys Gly 145 150 156 Lys Asp Lys Asp Thr Trp Ile Gln Cys Asn Lys Arg Asp Val Leu Cys 165 170 Gly Tyr Leu Leu Cys Thr Asn Ile Gly Asn Ile Pro Arg Leu Gly Glu 180 185 190 Leu Asp Gly Glu Ilio Thr Ser Thr Leu Val Val Gla Gla Gly Arg Thr Leu Asn Cys Ser Gly Gly His Val Lys Leu Glu Glu Asp Val Asp Leu 210 215 220 Gly Tyr Val Glu Asp Gly Thr Pro Cys Gly Pro Gln Het Met Cys Leu 230 235 Glu His Arg Cys Leu Pro Val Ala Ser Phe Asn Phe Ser Thr Cys Leu 245 250 255 Ser Ser Lys Glu Gly Thr Ile Cys Ser Gly Asn Gly Val Cys Ser Asn 260 265 270 Gin Leu Lys Cys Val Cys Asn Arg Ris Trp Ile Gly Ser Asp Cys Asn 275 280 Thr Tyr Phe Pro His Asn Asp Asp Ala bys Thr Gly Ile Thr Leu Ser 290 295 300 300 Gly Asn Gly Val Ala Gly Thr Asn Gly Ser Cys Asp Lys Thr His Thr 305 310 315 Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe 325 335 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val 355 360 365 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr 370 380 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val 388 390 395 Leu Thr Val Leu His Gln Asp Trp Leu Asu Gly Lys Glu Tyr Lys Cys 410 Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser

425

```
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
                                         440
                                                                445
          Ser Arg Asp Glu Leu Thr Lys Asn Gln Vel Ser Leu Thr Cys Leu Val
450 455
5
          Lys Gly Phe Tyr Pro Ser Asp Ile Ala Wal Glu Trp Glu Ser Asn Gly
                                 470
                                                       475
                                                                             480
          455
          Gla Pro Glu Asn Asa Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                            485
                                                490
          Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                        508
                                             505
10
          Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
                  515
                                        520
                                                            525
          Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
               530
                                     535
15
          <210> 17
          <211> 1668
          <212> DNA
           <213> Artificial Sequence
          <228×
2/2
           <223> Description of Artificial Sequence: fusion
                 polypeptide
          <228×
           <221> CDS
          <222> {25}..(1647)
25
           <400> 17
          gtogacccaa gotggotago caco atg gag aca gad aca oto otg cta tgg
                                        Met Glu Thr Asp Thr Leu Leu Leu Trp
30
           gta ctg ctg ctc tgg gtt cta ggt tec act ggt act agt tgt gga aat
           Val Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Thr Ser Cys Gly Asn
           gga tac gtc gas gct ggg gag gag tgt gat tgt ggt ttt cat gtg gaa
Gly Tyr Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Phe Ris Val Glu
25
           tgo tat gga tta tgo tgt aag aam tgt too oto too aac ggg got cac
Cys Tyr Gly Lew Cys Cys Lys Lys Cys Ser Lew Ser Asn Gly Wla His
                                                                                     195
40
                                                                                     243
           tge age gac ggg ecc tge tgt aac aat acc tea tgt ett ttt cag coa
           Cys Ser Asp Gly Pro Cys Cys Asn Asn Thr Ser Cys Leu Phe Gln Pro
           cga ggg tat gaa tgc cgg gat gct gtg aac gag tgt gat att act gaa
Arg Gly Tyr Glu Cys Arg Asp Ala Val Asn Glu Cys Asp Ile Thr Glu
                                                                                     291
48
           tat tgt act ggs gac tet ggt cag tgc cca cca aat ctt cat aag caa
                                                                                     339
           Tyr Cys Thr Gly Asp Ser Gly Gln Cys Pro Pro Asn Leu His Lys Gln
                                                        200
           gar gge tat gra tgr mat can ant cay gge ege tge tac mat gge gag
           Asp Gly Tyr Ale Cys Aso Gln Asn Gln Gly Arg Cys Tyr Asn Gly Glu
           tgc ang gcc aga gac aac cag tgt cag tec atc tgg gga aca aag gct
           Cys Lys Ala Arg asp Asn Gln Cys Gln Tyr Ile Trp Gly Thr Lys Ala
                         125
                                              130
```

					eaç Lys												483
§	gag Glu	aag Lys 155	Gly Gly	aac Asq	tgc Cys	gly ggg	aag Lys 160	gat. Asp	gga Gly	gac Asp	yra caa	tgg Trp 165	att Ile	cag Gln	tgc Cys	agc Ser	531
10	aaa Lys 170	cat His	gat Asp	gtg Val	ttc Phe	tgt Cys 175	gga Gly	tte Phe	tta Leu	ctc Leu	tgt Cys 180	acc Thr	aat Asn	ctt Leu	act. Thr	ega Arg 185	579
					ggt Gly 190												627
15					cgg Arg												675
20	gat Asp	gat Asp	gat Asp 220	acg	gat Asp	gtg Val	GIY ggc	tat Tyr 225	gta Val	gaa Glu	gat Asp	gga Gly	acg Thr 230	cca Pro	tgt Cys	Gly	723
					tgt Cys												771
25					tgt Cys												819
302					agt Ser 270												867
					tgc Cys												915
38	Pro	aag Lys	gat Asp 300	Glu	Gly	Pro	aag Lys	ggt Gly 305	Pro	øgt Ser	goc	acc Thr	aat Asn 310	aga Arg	tet Ser	cys	963
40	gac Asp	Lys 315	Thr	cac His	Thr	tgc Cys	eca Pro 320	Pro	tgc Cys	Pro	gca Als	cet. Pro 325	gaa Glu	gcc	gag Glu	gge Gly	1011
	gcg Ala 330	Pro	Ser	gtc Val	Phe	Leu 335	Phe	Pro	Pro	Lys	Pro 340	eag Lys	gac Asp	acc	Leu	atg Met 345	1059
45	ato	s ser	Arg	Thr	Pro 350	Glu	gtc Val	Thr	tgc Cys	grg Val 355	gtg Val	gtg Val	gac Asp	gtg Val	ser 360	cac His	1107
50					gtc Val					Tyr							1155
	cat	aat Asc	gcc Ala 380	Lys	ace Thr	aag Lys	ceg	egg Arg 385	Glu	gag Glu	cag Gln	tac Tyr	aac Asn 390	age Ser	acg	tac Tyr	1203
55	cgg	gte	gte	age	gto	ctc	acc	gtq	ctg	cac	cag	gac	tgg	ctg	sat.	gga	1251

	Arg Val Val Ser Val Leu Thr Val Leu His Glm Asp Trp Leu Asn Gly 395 400 405	
š	asy gay tan asy byo asy gire too aan aas yoo oto cos goo oso ato lys Glu Tyr Lys Cys Lys Val Ser Asm Lys Als Leu Pro Ale Pro Ile 410	1299
10	gag aas acc atc toc aas goc aas ggg cag occ cga gas cos cag gtg Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val 430	1347
	tac acc ctg ecc oca toc egg gat gag etg acc aag aac cag gte age. Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Glu Val Ser 450	1395
15	chg acc bgc chg gtc aaa ggc the bat oee age gwc atc gcc gtg gag Low Thr Cys Low Val Lys Gly Phe Tyr Pro Ser Aap Ile Ala Val Glw 453 470	1443
20	tgg gag âgc dat ggg cag cog gag dac duc tac dag dec dec cec Tr Clu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro 485 485	1491
	gig etg gac toe gac got too the the etc the age ang one ace gig Val Lem Asp Ser Amp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val 490 500 500	1539
25	gac aag agc agg tgg cag eag gag mac gto tto toa tgc too gtg atg hsp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met 510 515 520	1587
	cat gag get etg cac aac cac tac acg cag aag age etc tec etg tet His Olu Ala Leu His Asn His Tyr Thr Oln Lys Ser Leu Ser Leu Ser 525	1635
30	ccg ggt ama tgm actmgmagcgg ccgctacagm t Pro Gly Lys 540	1668
35	<210> 18 4313-540 4315-540 4315-540 4315-540 4315-540 4315-540 4315-540 4315-540 431	
40		
	<400> 18 Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro 1 5 10 15	
	Gly Ser Thr Gly Thr Ser Cys Gly Asn Gly Tyr Vel Glu Ala Gly Glu 20 25 30	
45	Glu Cys Asp Cys Gly Fhe His Val Glu Cys Tyr Gly Leu Cys Cys Lys 35 40 45	
	Lys Cys Ser Leu Ser Asn Gly Ala Ris Cys Ser Asp Gly Pro Cys Cys	
	Asn Asn Thr Ser Cys Leu Phe Gln Pro Arg Gly Tyr Glu Cys Arg Asp 55 75 80	
50	Ala Val Asn Glu Cys Asp Ile Thr Glu Tyr Cys Thr Gly Asp Ser Gly	
	Cln Cys Pro Pro Asn Leu His Lys Gin Asp Gly Tyr Ala Cys Asn Gin 100 105 110	
	Asn Glm Gly Arg Cys Tyr Asn Gly Glu Cys Lys Ala Arg Asn Gln	
85	Cys Gin Tyr lie Trp Gly Thr Lys Ala Ala Gly Ser Asp Lys Phe Cys 136 140	

S

35

48

<400> 19 Arg Gly Asp

```
Tyr Glu Lys Leu Asn Thr Glu Gly Thr Glu Lys Gly Asn Cys Gly Lys
                          150
                                                    155
           Asp Gly Asp Arg Trp Ile Gln Cys Ser Lys His Asp Val Phe Cys Gly
165 170 175
           Phe Leu Leu Cys Thr Asn Leu Thr Arg Ala Pro Arg Ile Gly Gln Leu
180 190
           Gln Gly Glu Ile Ile Pro Thr Ser Phe Tyr His Gln Gly Arg Val Ile
195 200 205
           Asp Cys Ser Gly Ala His Val Val Leu Asp Asp Asp Thr Asp Val Gly
               210
                                  215
                                                        220
           Tyr Val Glu Asp Gly Thr Pro Cys Gly Pro Ser Met Met Cys Lou Asp
                               230
                                                   235
           Arg bys Cys Leu Gin Ile Gin Ala Leu Asn Met Ser Ser Cys Pro Leu
                          245
                                     250
           Asp Ser Lys Gly Lys Val Cys Ser Gly His Gly Val Cys Ser Asn Glu
260 265 270
           Ala Thr Cys Ile Cys Asp Phe Thr Trp Ala Gly Thr Asp Cys Ser Ile
275 280 285
           Arg Asp Pro Val Arg Asn Leu His Pro Pro Lys Asp Glu Gly Pro Lys
                                   295
                                                        300
           Gly Pro Sor Ala Thr Asn Arg Ser Cys Asp Lys Thr His Thr Cys Pro
305 310 315
20
           Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe
325 330 335
           Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                                           345
           Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe 355 360 365
95
           Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
           Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Vel Ser Vel Leu Thr
                                                    395
           Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
405 410 415
           Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
                       420
                                            425
           Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
435 440
           Asp Clu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
           Phe Tyr Pro Sex Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
                                                    475
           Glu Asm Asm Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
485 490 495
            Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln 500 505 510
           Gly Asm Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asm His
                                      520 525
           Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                                    535
           <210> 19
           <211> 3
            <212> PRT
           <213> Artificial Sequence
           2220×
            <223> Description of Artificial Sequence: Consensus
                 binding motif
```

```
<210> 20
             <211> 67
             <212> PRT
             <213> Artificial Sequence
6
             <220>
             <223> Description of Artificial Sequence: consensus
                  disintegrin domain
             <220>
10
             <221> VARIANT
             <222> (5)..(9)
             <223> 3-5 varying residues in a consensus sequence
             <220>
             <221> VARIANT
15
             <222> (11)..(16)
             <223> 3-6 varying residues in a consensus sequence
             <220>
             <221> VARIANT
             <222> (19)..(22)
             <223> 2-4 varying residues in a consensus sequence
20
             <220>
             <221> VARIANT
             <222> (24)..(36)
<223> 7 varying residues in a consensus sequence
25
             <2220>
             <221> VARTANT
             <222> (32)..(37)
             <223> 4-6 varying residues in a consensus sequence
            <220>
322
             <221> VARIANT
             <222> (40).. (43)
             <223> 2-4 varying residues in a consensus sequence
             <220>
             <221> VARIANT
38
             <222> (45)..(52)
             <223> 8 varying residues in a consensus sequence
             <220>
             <221> VARIANT
             <222> (54)., (60)
40
             <223> 5-7 varying residues in a consensus sequence
             <228>
             <221> VARIANT
             <222> (62)..(66)
             <223> 3-5 varying residues in a consensus sequence
48
             <400> 20
             Cys Asp Cys Gly Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa
             Cys Cys Xea Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
40
             Xaa Xaa Xaa Xaa Xaa Cys Cys Xas Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
            Kaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
55
```

	Xaa 65	Xaa	Cys														
5																	
-5	<210	> 25															
	<211																
	<212																
			tífi	cial	Seç	pienc	48										
10	<220																
	<223		scri			Art	ific	ial	Segu	ence	e; £	sior	1				
	<220																
	<223		25														
15			18).	. (17	(201												
	<400																
	gggt	tete	sec s	gtes	cgac	g ti	gtas	iaacç	ace	gcca	agtg	aatt	gtar	ata (cgact	cacta	60
	tagg	gege	at t	gggt	accç	g gc	ccc	ccto	gae	gtc	gace	caag	getg	gct	sgcca	DOC	11.7
20	atg	gag	aca	gac	aca	ata	ctg	eta	tgg	gta	ctg	ctg	ctc	tgg	gtt.	cea	165
	Met 1	Glu	Thr	Asp	Thr 5	ren	Leu	Lea	Trp	Val 10	Leu	rea	Leu	Trp	Val 15	Pro	
	nert	tec	act	nat	art	tne	tgt	non	aat	not	ate	art	gaa	ann	ma	man	213
25				Gly			Cys										
				20					25					30			
	gag	tgt	gac	tgt	gga	cct	tta	aag	cat	tgt	ğça	888	gat	ccc	tgc	tgt	261
	Glu	Cys		Cys	es à	Pro	Leu		His	Cys	Ala	Lys	Asp	Pro	Cys	Cys	
			35					40					45				
30	ctg	tea	aat	tgc	act	ctg	act	gat	ggt	ret	act	tat	get	ttt	dad	ctt	309
	Leu		Asn	Cys	Thx	Leu	Thr	Asp	Gly	Ser	Thr		Ala	Phe	Gly	Leu	
		50					55					60					
	tgt	tgc	aaa	gac	tgc	aag	tte	cta	cca	tca	ggg	aaa	gtg	tgt	aga	aag	357
36	Cys	Cys	Lys	Asp	Cys	Lys	Phe	Leu	Pro	Ser	GIY	Lys	Val	Cys	Axg	Lys	
	65					70					75					80	
							cet										405
	Glu	Val	Asn	Glu	Cys 85	Asp	Leu	Pro	Glu	Trp	Cys	Asn	CIA	The	Ser 95	His	
#7																	
4-2	aag	tgc	cca	gat	gac	ttt	tat	gtg	gaa	gat	gga	att	ccc	tgt.	aag	gag	453
	PAs	Cys	Pro	100		Phe	TYX	vai	105	ASD	GIÃ	Tle	Pro	110	Lys	GLu	
				100					203					****			
	agg	ggc	tac	tgc	tat	gaa	aag	age	tgt	cat	gac	ege	aat	gaa	cag	tgt	501
		Clar	Tvr	CAs	Tyr	Glu	Lys	Ser	Cys	His	Asp	Arg	Asn	Glu	Gln	Cys	
417	Arg	10.23						120					125				
45	Arg		115														
45			115		ggt	gca	gge	gca	386	act	qça	agt	gag	act	tge	tac	549
45	agg	agg	115 att	ctt			ggc Gly					Ser					549
45	agg	agg	115 att	ctt													549
	agg	agg Arg 130	115 att	ttt. Phe	GLY	Ala	Gly	Ala	Asn	Thr	Ala	Ser 140	Glu	Thr	Cys	Tyr	549 597
	agg Arg asa Lys	agg Arg 130 gas Glu	115 att Tle	ttt Phe	Gly	Ala tta	Gly 135 ggt Gly	Ala	Asn	Thr	ggt Gly	Ser 140 cac	Glu	Thr	Cys	Tyr saa Lys	
	agg Arg	agg Arg 130 gas Glu	115 att Tle	ttt Phe	Gly	Ala	Gly 135 ggt Gly	Ala	Asn	Thr	Ala	Ser 140 cac	Glu	Thr	Cys	Tyr	
45 50	agg Arg ass Lys 145	agg Arg 130 gas Glu	115 att Ile ttg	ttt. Phe aac Asn	Gly acc Thr	Ala tta Leu 150	Gly 135 ggt Gly	Ala gac Asp	Asn egt Arg	Thr gtt Val	ggt Gly 155	Ser 140 cac His	Glu tgt Cys	Thr ggt Gly	Cys atc Ile	Tyr oaa Lys 160	
	agg Arg awa Lys 145	agg Arg 130 gas Glu	115 att Ile ttg Leu	ttt Phe acc Asn	acc Thr	tta Leu 150 aag	Gly 135 ggt Gly	Ala gac Asp	Asn cgt Arg	Thr gtt Val	ggt Gly 155	Ser 140 cac His	Glu tgt Cys	Thr ggt Gly	Cys atc Ile	Tyr saa Lys 160	597

	att	cag Gln	tgt Cys	gag Glu 180	aat Asn	gtg Val	Thr	gaa Glu	att Ile 185	Pro	aat Asn	atg Met	agt	gat Asp 190	cat His	act	693
5	act	gtg Val	cat His 195	tgg	get Ala	ege Arg	ttc Phe	ast Asn 200	gac Asp	ata	atg Net	tgc Cys	tgg Trp 205	agt Ser	net Thr	gat Asp	741
10	Tyr	Cat His 210	ttg Leu	61 A 88a	atg Met	aag Lys	gga Gly 215	cct Pro	gat Asp	att Tle	Gly	gas Glu 220	gtg Val	aaa Lys	gat	gga Gly	789
	aca Thr 225	gag Glu	tgt Cys	617 888	ata Tle	gat Asp 230	cat His	ata Ile	tge Cys	atc	Cac His 235	agg Arg	cac His	Cys	gtc Val	cat His 240	837
16	ite	Thr	atc	Leu	Asn 245	Ser	Asn	Cys	Ser	250	Ala	Phe	Ċλæ	Asn	Lys 255	Arg	885
30	GIA	116	tgc Cys	260	Asn	Lys	His	His	Cys 265	His	Cys	Asn	Tyr	Leu 270	Try	Asp	933
	PIO	gro	aac Asn 275	cys	Lea	He	Lys	280 Gly	TYX	GIÃ	Gly	Ser	Val 285	Asp	Ser	Gly	981
98	Pro	290	Pro	Lys	Arg	Lys	Lys 295	ŗàż	Lys	Lys	Arg	Ser 300	Cys	Asp	Lys	Thr	1029
. 30	305	Thr	tgc Cys	Pro	Pro	310 CA2	Pro	Ala	Pro	Glu	Ala 315	Glu	Cly	Ala	Pro	Ser 320	1077
	Va.l.	Phe	Leu	Phe	325	Sxo	Lys	Pro	Lys	Asp 330	Thr	Leu	Mec	Ile	Ser 335	Arg	1125
35	Thr	Pro	gag Glu	740	Thr	CÃê	Val	Val	Val 345	Asp	Val	Ser	His	Glu 350	Asp	Pro	1173
40	0113	407	aag Lys 355	rne	ASTI	Trp	lyr	368	Asp	Gly	Val	GLu	V&1 365	His	Asn	Ala	1221
	uys	370	aag Lys	Pro	Arg	Glu	G1u 375	Gln	Tyr	Asn	Ser	Thr 380	Tyr	Arg	Val	Val	1269
45	385	var	cte Leu	2335.	Vai	390	H1.5	GIE	qań	Trp	100 395	Asn	Gly	Lys	Glu	Tyr 400	1317
50	lys	t.gc Cys	aag Igs	gtc Val	ser 405	aac Asu	aaa Lys	gcc Ala	ctc Leu	cca Pro 410	gcc Ala	Pro	atc	gag Glu	aaa Lys 415	acc Thr	1365
	atc Ile	rcc Ser	aaa Lys	gee Ala 420	aaa Lys	G13 G33	cag Gln	ccc Pro	cga Arg 425	gaa Glu	cea Pro	cag Gln	Val	tac Tyr 430	acc Thr	ctg Leu	1413
55	ccc	CCS	toe	cgg	gat	gag	ctg	acc	aag	anc	cag	gtc	agc	ctg	acc	tgc	1461

ó

Pro	Pro	Ser 435	Arg	Asp	Glu	Leu	Thr 440	Lys	Asn	Gln	Val	Ser 445	Leu	Thr	Cys	
ctg Leu	gtc Val 450	asa Lys	gly	ttc Phø	tat Tyr	ecc Pro 455	agc Ser	gac Asp	atc Ile	gcc Ala	gtg Val 460	gag Glu	tgg Trp	gag Glu	agc Ser	1509
								aag Lys								1557
 ser	gac Asp	GJA āāc	tcc Ser	ttc Phe 485	tta Phe	etc Leu	tac Tyr	agc Ser	aag bys 490	ctc Leu	acc Thr	gtg Val	gac Asp	aag Lys 495	agc Ser	1605
agg	tog Trp	cag Gln	cag Gln 500	era êaa	aac Asn	gtc Val	tta Phe	tca Ser 505	tgc Cys	tec 8ex	gtg Val	atg Met	cat His 510	gag Glu	gct. Ala	1653
ctg	cac His	880 Asn 515	cac His	tac Tyr	acg Thr	cag Gln	aag Lys 520	agc Ser	cto Leu	ted Ser	ctg Leu	tot Ser 525	ccg Pro	ggt Gly	aaa Lys	1701
tga	act	agage	caa .	coge	tacas	ga t										1725
<21	0> 2 1> 5 2> P	26														
<21	3> A 3> D	rtif	ipti				cial	Seq	uence	ai fi) sio	n				
	0≻ 2 G1u		Aso	Thr	Lesu	Len	Leo	Trp	Val	Lou	Lins	Len	Trn	Val	Pro	
1				5				Asn	10					25		
			20					25					30			
		35					40	Ris				45				
	50					.55		Gly			68					
65					70			Pro		75					80	
Glu	. Val	Asn	Glu	Cys 85	Asp	Leu	Pro	Glu	Trp	Cys	Asn	Gly	Thr	Ser 95	His	
Lys	CAR	Pro	Asp 100		Phe	Tyr	Ve2	Glu 105	Asp	GJÅ	Ile	Pro	Cys 110	Lys	Glu	
Arg	Gly	Tyr 115		Tyr	Glu	Lys	Ser 120	Cys	His	Asp	Arg	Asn 125	Glu	Gln	СУв	
Arg	Arg	Ile		Gly	Ala	Gly 135	Ala	Asn	The	Ala	Ser 140		Thr	Cys	Tyr	
Lys 145	Glu		Asn	Thr	Leu 150	Gly		Arg	Val	Gly 155		Cys	Gly	Ile	Lys 160	
		Thr	Tyr	116	Lys		Asn	rle	Ser		Val	Gla	Cys	Gly		
Ile	Glr	Сув		Asn		The	Glu	Tle	Pro	Asn	Met	Sex		His	Thr	
The	. Val				Arg	Phe	Asn	185 Asp		Mec	Cys	Trp	190 Ser		Asp	
Tyr				Met	Lys	GLy	200 Pro	Asp	Ile	Gly		Z05 Val	Lys	Asp	Gly	
	210)				235		Cys			220					
225	,				230			Ser		235					240	
				245					250			,		255		

Gly Ile Cys Asn Asn Lys His His Cys His Cys Asn Tyr Leu Trp Asp 260 265 Pro Pro Asn Cys Leu Ile Lys Gly Tyr Gly Gly Ser Val Asp Ser Gly ă 275 280 285 Pro Pro Pro Lys Arg Lys Lys Lys Lys Arg Ser Cys Asp Lys Thr 290 295 300 300 His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Gle Gly Ala Pro Ser 305 310 315 320 Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg 325 330 335 10 Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro 340 345 350 Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala 355 360 365 15 Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr 385 390 400 Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr 405 410 415 20 The Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu 420 425 430 Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys 435 440 445 Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser 25 450 455 460 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp 470 475 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser 485 490 Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala 500 505 Leu Ris Asn Ris Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 515 520

35

40

45

SEQUENCE LISTING

	<110> Immunex Corporation	
	Fanslow, William C.	
5	Poindexter, Kurt	
	Cerretti, Douglas P.	
	Black, Roy A.	
	<120> INTEGRIN ANTAGONISTS	
20		
	<130> P34255EP1	
	<140> 3P06026259.9	
	<141> 2605-12-19	
15	<150> BP01920133.4	
	<151> 2001-02-23	
	<150> US60/184,865	
	<151> 2000-02-25	
80	<160> 22	
	£400× 62	
	<170> PatentIn Ver. 2.1	
	<210> 1	
26	<211> 1700	
	<212> DNA	
	<213> Artificial Sequence	
	<226>	
	<223> Description of Artificial Sequence: fusion	
SiO	polypeptide	
	* * * * * * * * * * * * * * * * * * * *	
	<330>	
	<221> CDS	
36	<222> (118)(1602)	
35	<406> 1	
	gggttttccc agtcacgacg ttgtamamog scggccagtg aattgtaata cgactcacta 60	
	addennesses edecendend codragged aridderwird eactitesacs edecreaces on	
	tagggrgast tgggtaccgg geccccccte gaggtegace caagetgget agccace 117	
40		
40	atg gag aca gac aca etc cig eta tgg gia cig cig etc tgg git cea 165	
	Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro	
	1 5 10 15	
	ggt bor act ggt act agt tgt ggg aac ctg ttt gtg gag cgt ggg gag 213	
45	Gly Ser Thr Gly Thr Ser Cys Gly Asn Leu Phe Val Glu Arg Gly Glu	
	20 25 30	
	cag tyc gad tyd ygd oed een yag yad tyd dyg aad ego tyd tyd aac 261	
	Gin Cys Asp Cys Gly Pro Pro Glu Asp Cys Arg Asn Arg Cys Cys Asn	
50	35 40 45	
	tet acc acc tgc cag etg get gag ggg gcc cag tgt geg cac ggt acc 309 Ser Thr Thr Cys Gln Leu Ala Glu Gly Ala Gln Cys Ala His Gly Thr	
	50 55 60	
	53 00	
55	tgc tgc cag gag tgc aag gtg aag ccg gct ggt gag ctg tgc cgt ccc 357	
	Cys Cys Gln Glu Cys bys Val Lys Pro Ala Gly Glu Leu Cys Arg Pro	

	65					70					75					80	
5	aag Lys	aag Lys	gae Asp	atg Met	tgt Cys 85	gac	ctc Leu	gag Clu	gag	ttc Phe 90	tgt Cys	gac	ggc Gly	egg	cac His	cct Pro	105
10	gag gag	tgc Cys	bro	gaa Glu 100	gac	gcc	ttc Phe	cag Gln	gag Glu 105	aac Asn	ggc	acg	Pro	tgc Cys 110	ter	gly aaa	453
	gly	tac Tyr	tgc Cys 115	tac Tyr	aac	993 Gly	gcc	tgt Cys 128	ecc Pro	acs Thr	ctg Leu	gcc Ala	cag Gln 125	cag Gln	tgc Cys	cag Gln	501
15	gco Ala	ttc Phe 130	tgg	G1A 888	pro	ggt Gly	999 Gly 135	cag Gln	gct Ala	gcc Ala	gag Glu	gag Glu 140	tcc Ser	tgc Cys	Phe	boc Ser	549
20	tat Tyr 145	gac Asp	atc	cta Leu	cca Pro	99c 61y 150	tga Cys	Lys	gcc	agc Ser	cgg Arg 155	tac	agg Arg	get Ala	gac Asp	atg Met 160	597
	tgt. Cys	gge Gly	gtt. Val	ctg Leu	caa Gln 165	tgt Cys	aaa Lys	Gly	ggt Gly	caa Gln 170	caa Gln	ect Pro	tta Leu	ggt Gly	aga Arg 175	gct Ala	645
25	ata Ile	tgt Cys	att	gtc Val 180	gac Asp	gtg Val	rgc Cys	cac His	gog Ala 135	ctc Leu	aec Thr	aca	gag Glu	gat Asp 190	ggc Gly	act Thr	693
30	gcg Ala	tat	gaa Glu 195	cca Pro	gtg Val	pro	gag Glu	ggc Gly 200	acc	cgg Arg	tgt Cys	gga Gly	cca Pro 205	gag Glu	aag	gtt Val	741
35	cys	tgg Trp 210	aaa Lys	gga Gly	cgt Arg	tgc Cys	cag Gln 215	gac Asp	tta Leu	caç His	gtt Val	tac Tyr 320	aga Arg	tec Ser	agc Ser	aac Asn	789
	cys 225	tct Ser	gec Ala	cag Gln	tge Cys	cae His 230	aac Asn	cat	Gly ggg	gtg Val	tgc Cys 235	aac Asn	cac His	aag Lys	cag Gln	gag Glu 240	837
40	tge Cys	cac His	tgc Cys	cac His	gcg Ala 245	ggc	tgg Trp	gcc Ala	eeg Pro	cec Pro 250	cac His	cys cys	gcg Ala	aag bys	ctg Leu 255	ctg Leu	885
45	act Thr	gag Glu	gtg Val	cac His 260	gca Ala	geg Ala	tcc Ser	61 y	aga Arg 265	tct Ser	tgt Cys	gac Asp	aaa Lys	act Thr 270	cac His	aca	933
	Cys	cca Pro	ceg Pro 275	rge Cys	cca Pro	gca Ala	cct Pro	gaa Glu 280	gec Ala	gag Glu	ggc Gly	geg Ala	ecg Pro 285	tca Ser	gtc Val	rtc Phe	981
50	ctc 1029 Leu											Ile					
άδ	gag	gtc	aca	tgc	gtg	gtg		gac	gtg	agc	cae	300 gaa	gac	cat	gag	gtc	

	Glu Val	The	Cys	Val	Val 310	Val	Asp	Val	Ser	His 315	Glu	Asp	Pro	Glu	Val 320	
5 -	aag tto 1125	aac	tgg	tac	gtg	gac	99c	gtg	gag	gtg	cat	aat	gee	aag	aca	
	Lys Phe	Asn	Trp	325	Val	Авр	Gly	Val	G1u 330	Val	His	Asn	Ala	Lys 335	Thr	
10	aag ocç	egg	gag	gag	cag	tac	aac	agc	acg	tac	cgt.	gtg	gtç	agc	gtc	
	Lys Pro	Arg	Glu 340	Glu	Gln	Tyr	Asn	Ser 345	Thr	Tyr	Arg	Val	Val 350	Ser	Val	
15	ctc acc	gtc	ctg	cac	cag	gac	tgg	ccg	aar	ggc	aag	gag	tac	aag	tgc	
	Leu Thr	741 355	Leu	His	Gln	Asp	Trp 360	Leu	Asn	Gly	Lys	Glu 365	TYY	Lys	Cys	
20	aag gto 1269	toa	aac	asa	gee	ccc	cca	gcc	ccc	atc	gag	aaa	acc	atc	tcc	
	Lys Val		Asn	Lys	Ala	Leu 375	Pro	Ala	Pro	lle	380	Lys	The	Ile	Ser	
	aas gcc					-	-		_				-			
25	Lys Ala	Lys	Gly	Gln	Pro 390	arg	Glu	Pro	Gln	Val 395	Tyr	Thr	Pen	Pro	Pro 400	
	tor ogg															
30	Ser Arg	Glu	Glu	Met 405	Thr	Lys	Asn	Gln	Val 410	Ser	Leu	Thr	Cys	Leu 415	Val	
	aaa ggc 1413	tte	tat	ecc	age	gac	atc	gcc	gtg	gag	tgg	gag	age	aat	aaa	
35	Lys Gly	Phe	Tyr 420	Pro	Ser	Asp	Ile	Ala 425	Val	Glu	Trp	Glu	Ser 430	Asn	Gly	
	cag ccg	gag	aac	aac	tac	aag	acc	acg	cet	ccc	gtg	ctg	gac	tcc	gac	
	Gln Pro	Glu 435	Asn	Asn	Tyr	Lys	Thr 440	Thr	Pro	Pro	Val	Leu 445	Asp	Ser	Asp	
40	gge ted	ttc	tte	ctc	tar	agc	aag	ctc	açe	gtg	gac	aag	agc	agg	tgg	
	Gly Sea		Phe	Leu	Tyr	Ser 455	Lys	Leu	Thr	Val	Asp 460	Lys	Ser	Arg	Trp	
45	cag cag	999	aac	gtc	tte	tca	tgc	tec	grg	atg	cat	gag	get	ctg	cac	
	Gln Glr 465	Gly	Asn	Val	Phe 470	ser	Cys	Ser	Val	Met 475	His	G) n	Ala	Leu	His 480	
50	aac cac	tac	acg	cag	aag	age	ctc	tcc	atg	tot	ccg	ggt	aaa	tga		
	Ass His	Tyr	Thr	Gln 485	Lys	Ser	Leu	Ser	Leu 490	Ser	Pro	Gly	Lys	495		
56	actagaç	icgg :	ecge	caec	ge gg	gtgg	agot	c ca	getti	etgt	tec	ettr	agt (gaggg	grtaat	

ttogagettq gegtaateat ggtcataget qtttectq

<210> 2 <211> 494 <312> PRT <213> Artificial Sequence 10 <223> Description of Artificial Sequence: fusion polypeptide <400> 2 Met Clu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Trp Val Pro 5 10 Gly Ser Thr Gly Thr Ser Cys Gly Asn Leu Phe Val Glu Arg Gly Glu 20 25 Gln Cys Asp Cys Gly Pro Pro Glu Asp Cys Arg Asn Arg Cys Cys Asn 35 40 20 Ser Thr Thr Cys Glm Leu Als Glu Gly Als Gln Cys Ala His Gly Thr 55 Cys Cys Gln Glu Cys Lys Val Lys Pro Ala Gly Glu Leu Cys Arg Pro 75 76 Lys Lys Asp Met Cys Asp Leu Glu Glu Phe Cys Asp Gly Arg His Pro 85 90 25 Glu Cys Pro Glu Asp Ala Phe Gln Glu Asn Gly Thr Pro Cys Ser Gly 300 105 116 Gly Tyr Cys Tyr Asn Gly Als Cys Pro Thr Leu Als Gln Gln Cys Gln 3.15 120 125 Als Phe Trp Gly Pro Gly Gly Gln Ala Ala Glu Glu Ser Cys Phe Ser 3/3 130 135 140 Tyr Asp Ile Leu Pro Gly Cys bys Ala Ser Arg Tyr Arg Ala Asp Met 145 150 155 160 Cys Gly Val beu Gln Cys Lys Gly Gly Gln Gln Pro Leu Gly Arg Ala 165 1.70 175 36 Ile Cys Ile Val Asp Val Cys His Ala Leu Thr Thr Glu Asp Gly Thr 180 185 190 Ala Tyr Glu Pro Val Pro Glu Gly Thr Arg Cys Gly Pro Glu Lys Val 200 Cys Trp Lys Gly Arg Cys Gln Asp Leu His Val Tyr Arg Ser Ser Asn 210 215 220 Cys Ser Ala Gln Cys His Asn His Gly Val Cys Asn His Lys Gln Glu 230 235 Cys His Cys His Ala Gly Trp Ala Pro Pro His Cys Ala Lys Leu Leu 245 250 255 Thr Glu Val His Ala Ala Ser Gly Arg Ser Cys Asp Lys Thr His Thr 250 45 265 Cys Pro Pro Cys Pro Ale Pro Glu Ala Glu Gly Ala Pro Ser Val Phe 280 285 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro 295 300 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val 315 310 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr 330 335 325 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val 345 350 Leu Thr Val Leu His Glu Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys 360

	Lys	7a.l 370	Sex	Asn	Lys	Ala	Leu 375	Pro	Ala	Pro	Tle	380	Lys	Thr	ile	Ser	
	Lys 365	Ala	Lys	Gly	Gln			Glu	Pro	Glo			Thx	beu	Pro		
ő		Arres	Glu	Gin	Mart	390	Tarre	Non-	(21 m	Ma I	395	T 011	77% ve	Our	ron	400	
	UL.	100,3		0.00	405	2752	wyw	750	9111	410	Ser	men	1111	cye	415	AST	
	Lys	$G1_Y$	Phe	Tyr 420	Pro	Ser	Asp	Ile	Ala 425	Val	Glu	Trp	Glu	Ser 430		G33	
	Gln	Pro	Glu		Asn	Tyr	Lvs	Thr			Pro	Val	Leu		Ser	Aso	
10			435					440					445				
	Gly	5er 450	Phe	Phe	Leu	Tyr	Ser 455	Lys	Leu	Thr	Val	Asp 460	Lys	Ser	Arg	Trp	
		Gln	Gly	Asn	Val		Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	
	465	m: -	<i>(</i> 10, 11)	en	es V	470					475					480	
18	W911	11.2.5	Tyr	1191	485	uys	ser	Little	ser	490	Ser	Pro	GIĀ	rys			
	<21	0 > 3															
		1> 1-															
20		2> Di 3> A:	NA rtif	icía.	l Se	quen	ce										
	<23	3 > D	eser.			f Ar	tifi	cial	Segi	uenc	o: £1	usio	n				
26	<22	0.															
	<22	1> C1	DS 46).	. (1.6	17)												
.90		3 د0															
36			ggc ·	ecce	cete	ga ge	areg	acco	á ag	ctgg	rtag	cca				ca gac	
36			ggc	0000	cete	ga ge	greg	acco.	á ag	ctgg	rtag	cca				ca gac ar Asp	
36	ggti	accg											M	st G	lu T	ar Asp	
36	ggt	ctc	ggc ctg Leu	cta	tgg	gta Val	etg	ctg	ctc	tqq	gtt Val	cca	qqt	tcc	lu Ti	ggt Gly	
	aca Thr	ctc Leu	ctg	cta Leu	tgg Trp	gta Val 10	etg Leu	ctg Leu	ctc Leu	tgq Trp	gtt Val 15	cca Pro	ggt	tcc Ser	act Thr	ggt Gly 29	105
	aca Thr 5	ctc Leu	ctg Leu	cta Leu ggt	tgg Trp	gta Val 10	etg Leu	ctg Leu	ctc Leu gac	tgg Trp get	gtt Val 15	cca Pro	ggt Gly gag	toc Ser	act Thr	ggt Gly 20 tgt	
35	aca Thr 5	ctc Leu	ctg	cta Leu ggt	tgg Trp	gta Val 10	etg Leu	ctg Leu	ctc Leu gac	tgg Trp get	gtt Val 15	cca Pro	ggt Gly gag	toc Ser	act Thr	ggt Gly 20 tgt	105
	aca Thr 5 act Thr	ctc Leu agr	etg Leu tgt Cys	cta Leu ggt Gly	tgg Trp aat Asn 25	gta Val 10 aag Lys	etg Leu ttg Leu	ctg Leu gtg Val	ctc Leu gac Asp	tgg Trp gct Ala 30	gtt Val 15 999 Gly	cca Pro gaa Glu	ggt Gly gag Glu	toc Ser tgt Cys	act Thr gac Asp	ggt Gly 20 tgt Cys	105
35	ggt: aca Thr 5 act Thr	ctc Leu agt ser	ctg Leu	cta Leu ggt Gly	tgg Trp aat Asn 25	gta Val 10 sag Lys	etg Leu ttg Leu	ctg Leu gtg Val	ctc Leu gac Asp	tgg Trp get Ala 30	gtt Val 15 999 Gly	cca Pro gas Glu tgc	ggt Gly gag Glu	toc Ser tgt Cys	act Thr gac Asp 35	ggt Gly 20 tgt Cys	105
35	aca Thr 5 act Thr Gly	ctc Leu agr ser act	crg Leu tgr Cys	cta Leu ggt Gly sag Lys 40	tgg Trp aat Asn 25 gaa Glu	gta Val 10 sag Lys tgt Cys	ctg Leu ttg Leu gas Glu	ctg Leu gtg Val ttg Leu	ctc Leu gac Asp gac Asp	tgg Trp gct Ala 30 cct Pro	gtt Val 15 999 Gly tgc Cys	cca Pro gaa Glu tgc Cys	ggt Gly gag Glu gaa Glu	tcc Ser tgt Cys 99a 61y 50	act Thr gac Asp 35 agt Ser	ggt Gly 29 tgt Cys	105
35	aca Thr 5 act Thr ggc Gly	ctc Leu agr ser act Thr	etg Leu tgr Cys eca Pro	cta Leu ggt Gly aag Lys 40	tgg Trp aat Asn 25 gaa Glu tca	gta Val 19 sag Lys tgt Cys	etg Leu ttg Leu gaa Glu	ctg Leu gtg Val ttg Leu gag Glu	ctc Leu gac Asp gac Asp	tgg Trp gct Ala 30 cct Pxc	gtt Val 15 999 Gly tgc Cys	cca Pro gaa Glu tgc Cys	ggt Gly gag Glu gaa Glu	tcc Ser tgt Cys gga Gly 50	act Thr gac Asp 35 agt Ser	ggt Gly 29 tgt Cys acc Thr	105
35	aca Thr 5 act Thr ggc Gly	ctc Leu agr ser act Thr	erg Leu tgr Cys eca Pro	cta Leu ggt Gly aag Lys 40	tgg Trp aat Asn 25 gaa Glu tca	gta Val 19 sag Lys tgt Cys	etg Leu ttg Leu gaa Glu	ctg Leu gtg Val ttg Leu	ctc Leu gac Asp gac Asp	tgg Trp gct Ala 30 cct Pxc	gtt Val 15 999 Gly tgc Cys	cca Pro gaa Glu tgc Cys	ggt Gly gag Glu gaa Glu	tcc Ser tgt Cys gga Gly 50	act Thr gac Asp 35 agt Ser	ggt Gly 29 tgt Cys acc Thr	105
35	aca Thr 5 act Thr Gly	ctc Leu agr ser act Thr	erg Leu tgr Cys eca Pro	cta Leu ggt Gly aag Lys 40 aaa	tgg Trp aat Asn 25 gaa Glu tca Ser	gta Val 10 aag Lys tgt Cys	etg ieu ttg Leu gaa Glu gct	ctg Leu gtg Val ttg Leu gag Glu 60	gac Asp gac Asp tgc	tgg Trp gct Ala 30 cct Prc	gtt Val 15 999 Gly tgc Cys	cca Pro gaa Glu tgc Cys	gag Glu gaa Glu gac Asp	tcc Ser tgt Cys gga Gly 50 tgt Cys	act Thr gac Asp 35 agt Ser tgt	ggt Gly 20 tgt Cys acc Thr	105 153 201 249
35 40 46	aca Thr 5 act Thr Gly cgt Cys	ctc Leu agt Sar act Thr ang Lys	etg Leu tgr Cys eca Pro	cta Leu ggt Gly sag Lys 40 saa Lys	tyg Trp sat Asn 25 gas Glu tes Ser	gta Val 10 sag Lys tgt Cys	etg Leu ttg Leu gaa Glu gct Ala	ctg Leu gtg Val ttg Leu gag Glu 60	ctc Leu gac Asp gac Asp tgt Cys	tgg Trp get Ala 30 cet Pro	gtt Val 15 998 Gly tgc Cys	eca Pro gaa Glu tgc Cys ggt Gly cga Arg	ggt Gly gag Glu gas Glu gas Asp 65	tcc Ser tgt Cys gga Gly 50 tgt Cys	act Thx gac Asp 35 agt Ser tgt Cys	ggt Gly 20 tgt Cys acc Thr aaa Lys	105
35	aca Thr 5 act Thr Gly cgt Cys	ctc Leu agt Ser act Thr	ctg Leu tgr Cys cca Pro	cta Leu ggt Gly sag Lys 40 saa Lys	tyg Trp sat Asn 25 gas Glu tes Ser	gta Val 10 sag Lys tgt Cys	etg Leu ttg Leu gaa Glu get Ala	ctg Leu gtg Val ttg Leu gag Glu 60	ctc Leu gac Asp gac Asp tgt Cys	tgg Trp get Ala 30 cet Pro	gtt Val 15 998 Gly tgc Cys	eca Pro gaa Glu tgc Cys ggt ggt	ggt Gly gag Glu gas Glu gas Asp 65	tcc Ser tgt Cys gga Gly 50 tgt Cys	act Thx gac Asp 35 agt Ser tgt Cys	ggt Gly 20 tgt Cys acc Thr aaa Lys	105 153 201 249
35 40 46	aca Thr 5 act Thr Giy tgt Cys	ctc Leu agr Ser act Thr aag Lys	ctg Leu tgr Cys cca Pro ett Leu 55	cta Leu ggt Gly sag 40 saa Lys	tgg Trp aat Asn 25 gas Glu tes Ser ett Leu	gta Val 10 sag Lys tgt Cys ttt Phe	etg ieu ttg Leu gas Glu gct Als Gly 75	ctg Leu gtg Val ttg Leu gag Glu 60 ggt	gac Asp gac Asp 45 tgt Cys	tgg Trp get Ala 30 cet Pro gea Ala tta Leu	gtt Vai 15 938 Gly tgc Cys tat Tyr	eca Pro gaa Glu tgc Cys egt Gly ega Arg	ggt Gly gag Glu gas Glo gas Asp 65	tcc Ser tgt Cys gga Gly 50 tgt Cys	act Thr gac Asp 35 agt Ser tgt Cys	ggt Gly 20 tgt Cys acc Thr ass Lys	105 153 201 249
35 40 46	aca Thr 5 act Thr Gly tgt Cys gac Asp	ctc Leu agt ser act Thr aag Lys tgt tgt tgt tgt tgt	ctg Leu tgr Cys cca Pro ett Leu 55 cgg Arg	cta Leu ggt Gly sag 40 sas Lys ttc Phe	tgg Trp sat Asn 25 gas Glu tes Ser ett Les	gta Val 10 sag Lys tgt Cys ttt Phe	etg ieu ttg Leu gaa Glu get Ala 99a Gly 75	ctg Leu gtg Val ttg Leu gag Glu 60 ggt Gly	ctc Leu gac Asp gac Asp 45 tgt Cys	tgg Trp gct Ala 30 cot Pro gca Ala tta Leu	gtt Val 15 999 Gly tgc Cys tat Tyr tgc	cca Pro gaa Glu tgc Cys ggt Gly cga Arg 80	ggt gly gag Glu gaa Glu gac Asp 65	tcc Ser tgt Cys gga gfy 50 tgt Cys	act Thr gac Asp 35 agt Cys	ggt Gly 20 tgt Cys sec Thr sea Lys agt cag	105 153 201 249
35 40 46	aca Thr 5 act Thr Gly tgt Cys gac Asp	ctc Leu agt ser act Thr aag Lys tgt tgt tgt tgt tgt	ctg Leu tgr Cys cca Pro ett Leu 55	cta Leu ggt Gly sag 40 sas Lys ttc Phe	tgg Trp sat Asn 25 gas Glu tes Ser ett Les	gta Val 10 sag Lys tgt Cys ttt Phe	etg ieu ttg Leu gaa Glu get Ala 99a Gly 75	ctg Leu gtg Val ttg Leu gag Glu 60 ggt Gly	ctc Leu gac Asp gac Asp 45 tgt Cys	tgg Trp gct Ala 30 cot Pro gca Ala tta Leu	gtt Val 15 999 Gly tgc Cys tat Tyr tgc	cca Pro gaa Glu tgc Cys ggt Gly cga Arg 80	ggt gly gag Glu gaa Glu gac Asp 65	tcc Ser tgt Cys gga gfy 50 tgt Cys	act Thr gac Asp 35 agt Cys	ggt Gly 20 tgt Cys sec Thr sea Lys agt cag	105 153 201 249
35 40 46	aca Thr 5 act Thr Gly Egs Cys Ess Glu 85	ctc Leu agt Ser act Thr agg bys tgt cys 70 tgt cys	ctg Leu tgr Cys cca Pro ett Leu 55 cgg Arg	cta Leu ggt Gly sag 40 saa Lys tro Phe	tgg Trp aat Asn 25 gaa Glu tes Ser ett Leu	gta Val 10 sag Lys tgt Cys ttt Phe cca Pro	ctg ieu ttg Leu gaa Glu gct Ala Gly 75 tac Tyr	ctg Leu gtg Val ttg Glu 60 ggt Gly	ctc Leu gac Asp gac Asp 45 tgt Cys act Thr	tgg Trp gct Ala 30 cct Prc gca Ala tta Leu	gtt Val 15 938 Gly tgc Cys tat Tyr tgc Cys	cca Pro gaa Glu tgc Cys ggt Gly cga Arg 80 tct Ser	ggt Gly gas Glu gac Asp 65 ggs Gly cag Gln	tgt Cys gga Gly 50 tgt Cys aaa Lys ttc Phe	act Thr gac Asp 35 agt Ser tgt Cys tgt Cys	ggt Gly 20 tgt Cys acc Thr acc Thr acc Thr acc Thr	105 153 201 249

	Pro	Asp	val	Phe	105	Gln	Asn	Gly	Tyr	Pro 110	Cys	Gln	Asn	Asn	1.ys	Ala	
ĕ					ggc Gly												441
10					ana Lys												489
					ggt Gly												537
16					tgt Cys												585
80					caa Gln 185												633
25					agt Ser												681
					ght Val												729
307					Lys												777
35					gac												825
40					aat Asn 265												873
					act Thr												921
45	aca Thr	tac Tyr	aat Asn 295	gaa Glu	Met	aat Asn	act Thr	gca Ala 300	ttg Leu	agg	gac Asp	gga Gly	ser 305	tgt Cys	gac Asp	aaa Lys	969
	act 101		aca	tge	cca	cag	tgc	cca	gca	cct	gaa	gcc	gag	ggc	geg	ccg	
50	Thr	Ris 310			Pro		315					320		·			
	tca 106		ttc	ctc	ttc	ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	atc	tee	
55	Ser 325	Val	Phe	Leu	Phe	Pro 330	Pro	Lys	Pro	Lys	Asp 335	Thr	Leu	Met	Ile	Ser 340	

		cgg acc	cct	gag	gtc	aca	rgc	gtg	gtg	gtg	gac	gtg	age	cac	gaa	gac	
	8	Arg Thr	Pro	Glo	Val 345	Thr	Cys	va)	Va)	Val 350	Asp	Val	Ser	His	Glu 355	Asp	
		cct gag	gtc	aag	tte	aac	ugg	tac	gtg	gac	ggc	gtg	gag	gtg	cat	aat	
	10	Pro Glu	Val	Lys 360	Phe	Asn	Trp	Tyr	Val 365	Asp	Gly	Val	Glu	Va1 370	His	Asn	
		gcc aag 1209	ă¢ā	aag	cog	cgg	gag	gag	cag	tac	aac	age	acg	tac	cgg	gtg	
		Ala Lys	Thr 375	Lys	Pro	Arg	Glu	Glu 380	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	
	15	gtc age	gre	ctc	acc	gte	ctg	cac	cag	gac	bgg	ctg	aat	gga	aag	gag	
		1257 Val. Ser 390	Val	Leu	Thr	Val	Leu 395	His	Gln	Asp	Trp	Leu 400	Asn	Gly	Lys	Glu	
	20	tac aag	tgo	aag	gte	tee	aac	aaa	gce	cto	cca		cac	atc	qaq	888	
		1305 Tyr Lys 405															
	25	acc atc	tec	aaa	gcc	aaa	999	cag	ccc	cga	gaa	cca	cag	gtg	tac		
		Thr Ile	Ser	Lys	Ala 625	Lys	Gly	Gln	Pro	Ang 430	Glu	Pro	Gln	Val	Tyr 435	Thr	
	90	etg ccc 1401	cca	tec	cgg	gat	gag	ctg	acc	aag	aac	cag	gtc	age	ctg	acc	
		Leu Pro	Pro	Ser 440	Arg	Авр	Glu	Leu	Thr 445	Lys	Asn	Gln	Val	Ser 450	Leu	Thr	
	35	tge etg 1449	gte	aaa	gge	ttc	tat	ecc	age	gac	atc	gee	gtg	gag	tgg	gag	
		Cys Leu	Val 455	ьув	Gly	Phe	Tyr	Pro 460	Ser	Asp	Ile	Ala	Va.l. 465	GLu	Trp	Glu	
	40	age aat 1497	999	cag	ecg	gag	aac	aac	tac	aag	acc	acg	cct	ccc	gtg	ctg	
	*2	Ser Asn 470	Gly	Gln	Pro	Glu	Asn 475	Asn	Tyr	Lys	Thr	Thr 480	Pro	Pro	Val	Leu	
		gac toc 1545	gac	gge	tcc	tte	tte	ctc	tac	age	aag	ete	add	gtg	gac	aag	
	45	Asp Ser 485	Asp	Gly	Ser	Phe 490	Phe	Leu	Tyr	Ser	Lys 495	Leu	Thr	Val	Asp	Lys 500	
		age agg 1593	tgg	çag	cag	999	aac	gt.c	ttc	tca	tgc	tcc	gtg	atg	cat	gag	
	90	Ser Arg	Trp	Gln	Gln SGS	GIA	Asn	Val	Phe	Ser 510	Cys	Ser	Val.	Met	His 515	Glu	
		get etg 1641	cac	aac	cac	tac	acg	cag	aag	age	arc	tec	ctg	tot	ccg	ggt	
4	85	Ala Leo	His	Ass 520	His	Tyr	Thr	Gln	Lys 525	Ser	Leu	Ser	Leu	Ser 530	Pro	Gly	

5

2%

92

36

40

45

```
aaa tga actagagogg cogctacaga t
           Liys
           <210> 4
           <213> 533
           <212> PRT
           <213> Artificial Sequence
10
           <223> Description of Artificial Sequence: fusion
                polypeptide
           <400× 4
95
           Met Glu Thr Asp Thr Leu Leu beu Trp Val Leu Leu Trp Val Pro
                                              10
           Gly Ser Thr Gly Thr Ser Cys Gly Asn Lys Leu Val Asp Ala Gly Glu
                       28
                                          25
                                                              30
           Glu Cys Asp Cys Gly Thr Pro Lys Glu Cys Glu Leu Asp Pro Cys Cys
20
                                      40
           Glu Gly Ser Thr Cys Lys Leu Lys Ser Phe Ala Glu Cys Ala Tyr Gly
                                  55
           Asp Cys Cys Lys Asp Cys Arg Phe Leu Pro Gly Gly Thr Leu Cys Arg
                               70
                                                  75
           Gly Lys Thr Ser Glu Cys Asp Val Pro Glu Tyr Cys Asn Gly Ser Ser
                           85
                                              90
           Gln Phe Cys Gln Pro Asp Val Phe Ile Gln Asn Gly Tyr Pro Cys Gln
                      300
                                         105
           Asn Asn Lys Als Tyr Cys Tyr Asn Gly Met Cys Gin Tyr Tyr Asp Ala
                                      120
                                                         125
           Gin Cys Gin Val Ile Phe Giy Ser Lys Ala Lys Ala Ala Pro Lys Asp
                                 135
                                                    140
           Cys Fhe Ile Glu Val Asn Ser Lys Gly Asp Arg Phe Gly Asn Cys Gly
           145
                             3.50
                                                155
           Phe Ser Gly Asn Glu Tyr Lys Lys Cys Ala Thr Gly Asn Ala Leu Cys
                         3 65
                                             170
           Gly Lys Leu Glu Cys Glu Asn Val Glu Glu Ile Pro Val Phe Gly Ile
                      180
                                        385
                                                            190
           Val Pro Ala Ile Ile Gln Thr Pro Ser Arg Gly Thr Lys Cys Trp Gly
                  195
                                     200
                                                        205
           Val Asp Phe Gin Leu Gly Ser Asp Val Pro Asp Pro Gly Met Val Asn
                                 215
                                                     220
           Glu Gly Thr Lys Cys Gly Ala Gly Lys Ile Cys Arg Asn Phe Gin Cys
           225
                             230 235
           Val Asp Ala Ser Val Leu Asm Tyr Asp Cys Asp Val Gln Lys Lys Cys
                          245
                                             250
           His Gly His Gly Val Cys Asn Ser Asn Lys Asn Cys His Cys Glu Asn
                               265
           Gly Trp Ala Pro Pro Asn Cys Glu Thr Lys Gly Tyr Gly Gly Ser Val
                   275
                                     280
                                                         285
           Asp Ser Gly Pro Thr Tyr Asn Glu Met Asn Thr Ala Leu Arg Asp Gly
                                  295
                                                     300
           Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Fro Glu Ala
                             310
                                                315
           Glu Gly Ala Pro Sex Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                          325
                                             330
           Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                      340
                                         345
           Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                                      360
                                                         365
```

G.	lu	Val.	Ris	Asn	Ala	Lys	Thr 375	Lys	Pro	Arg	Glu	Glu 380	Gln	Tyr	Asn	Ser	
79	ייי	Tur	Ara	Va 3	Va 3	Ser		3,011	Thr	W=1	1.2011		23 n	Asp	Ten	1	
	85	-,-	>			390		200	****		395	****	(0 1.14	wwh	i L L	400	
		220	7 ***	0711	The same		Cura	term	17m 3	~		Y	* 2 -				
85	315.5	ary	nys	CILL	405	Lys	Cys	pys	AST		ASU	ьys	818	Leu		Ala	
				_			_			410	_				415		
27	EO	116	610		THY	He	Ser	Lys		Lys	GIÀ	Gin	Pro	Arg	Glu	Pro	
				420					425					430			
G:	ln	Val		Thu	rest	bro	bro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	
			435					440					445				
Va	a.l	Ser	Leu	The	Cys	Leu	Val	Lys	Gly	Phe	Tyx	Pro	Ser	Asp	Ile	Ala	
		450					455	-	-			460					
Va	8.1	Glu	TYP	Glu	Ser	Agn	Glv	Gin	Pro	Glu	Assn	Ann	Tor	Lys	Thr	Thr	
46	65					470	•				475		-,-	1		480	
P	m	Pro	Val	Least	aen		Aen	123.22	cer	Dhe		Lance	*******	Ser	Tarm		
				200	485	001	arm's	0.4.1	201	490	FARG	mea.	LYL	Sex		Med	
cri)	h w	Y = (Y	***	Y		v	m	·**	m					-	495	-	
.11		A 500 T	พพบ		ಎಲ್	wag	rrb	U.L.D		GTA	San	val	rne	ser	Cys	Ser	
		**		500					505					510			
Va	ai	Met	His	Glu	ala	ren	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	
			515					520					525				
Le	BB.	Sex	Pro	Gly	Lys												
		530															
		> 5															
		. 24															
		> D)															
<2	213	A A	rt.i.f	icia)	E Sec	quenc	10										
K2	220																
<2			sacr	iptic	n of	E Art	ifi.	ial	Sem	enre	, fr	sice	,				
<2		> De		iptic		F Art	ifi	cial	Sequ	ence	ı fı	sica	ı				
<2		> De		iptic ptic		F Art	.1f1	cial	Sequ	ence	e: fi	sic	ı				
	323	> De				F Art	.1f1	cial	Sequ	sence	e: fi	sic	1				
<2	223	> De po	olype			F Art	:1f1	cial	Sequ	ence	e fi	sion	1				
<2 <2	223	i> De po i> i> Ci	olype os	eptic	ie	F Art	ifi:	cial	Sequ	sence	e fi	sica	1				
<2 <2	223	i> De po i> i> Ci	olype os		ie	F Art	ifi	cial	Sequ	ence	e fi	sica	1				
<2 <2 <2	223	> De > > > Cr > (3	olype os	eptic	ie	F Art	ifi	cial	Seqi	sence	e fi	sion	1				
<2 <2 <2	223	i> De po i> i> Ci	olype os	eptic	ie	F Art	ifi	cial	Seqi	sence	e: fu	sica	1				
<2 <2 <2 <4	223 221 222 800	> De pe > Cr > (2	01ype 08 25)	eptic	ie (2)									eta e	*fa i	aa	
<2 <2 <2 <4	223 221 222 800	> De pe > Cr > (2	01ype 08 25)	eptic	ie (2)		ROC A	ıtg ç	jag a	ica ç	gac a	ica c	nte d	etg c			
<2 <2 <2 <4	223 221 222 800	> De pe > Cr > (2 - - - - - - - - - - - -	01ype 08 25)	eptic	ie (2)		ROC A	itg ç fet 0	jag a	ica ç	gac a	ica c	nte d	otg o			
<2 <2 <2 <4	223 221 222 800	> De pe > Cr > (2 - - - - - - - - - - - -	01ype 08 25)	eptic	ie (2)		ROC A	ıtg ç	jag a	ica ç	gac a	ica c	nte d				10.0
44 42 43 43	223 221 222 100 100	i> De po	08 25)	. (142	ie i2) gotaç	ge ca	toe a	itg ç fet d	gag a	ica ç	gac s T qel	ica c Thr I	ete d	ieu l	eu :	rrp	
<2 <2 <4 gt	223 222 222 222 222 222	> De po	olype 08 25)	. (142 getgg	ie :2) sctac	ge ca	toc a	itg ç fet d	gag a	ica ç îhr 1	gac s lsp T	ica c hr I S	ete (tat	eu:	rp aat	
<2 <2 <4 gt gt Va	223 220 221 222 100 109	> De po	olype 08 25)	. (142 getgg	ie :2) sctac	grt Val	toc a	itg ç fet d	gag a	ica ç îhr 1	gac a ksp T ggt Gly	ica c hr I S	ete (ieu l	eu:	rp aat	
<2 <2 <4 gt gt Va	223 222 222 222 222 222	> De po	olype 08 25)	. (142 getgg	ie :2) sctac	ge ca	toc a	itg ç fet d	gag a	ica ç îhr 1	gac s lsp T	ica c hr I S	ete (tat	eu:	rp aat	
<2 <2 <4 gt gt Va	223 220 221 222 100 109	> De po	olype 08 25)	. (142 getgg	ie :2) sctac	grt Val	toc a	itg ç fet d	gag a	ica ç îhr 1	gac a ksp T ggt Gly	ica c hr I S	ete (tat	eu:	aat Asn	
44 9t Va Va	223 220 221 222 400 509	> De po	olype 08 25) caa (ctg Leu	eption (142) ctc Leu	ie (2) gotag tgg Trp	ge ca get Val	cca Pro	stg set of	sag a Slu T Ecc Ser	ca shr A	gac s usp T ggt Gly 20	ca c for I s act Thr	etc (eu 1 agt ser	tgt Cys	gga Gly	aat Asn 25	ş
<2 <2 <4 gt 9 7 9 8	223 220 221 222 400 509	> De po	olype 08 25) caa (ctg Leu	eptic .{142 gctgg ctc Leu	ie (2) gctag tgg Trp caa	ge ca get Val 15	cca Pro	stg see 6	gag a Blu 7 Ecc Ser	aca g Thr 3 act Thr	gac s usp T ggt Gly 20	ca c hr I s act Thr	etc (eu l agt ser	tgt Cys	gga Gly	aat Aan 25	ş
<2 <2 <4 gt 9 7 9 8	223 220 221 222 400 509	> De po	olype 08 25) caa (ctg Leu	eptic .{142 gctgg ctc Leu	is i2) gotac tgg Trp caa Gin	ge ca get Val 15	cca Pro	stg see 6	gag a Blu 7 Ecc Ser	act Thr gat Asp	gac s usp T ggt Gly 20	ca c hr I s act Thr	etc (eu l agt ser	tgt Cys	gga gly gac Asp	aat Aan 25	ş
<2 <2 <4 gt 9 7 9 8	223 220 221 222 400 509	> De po	olype 08 25) caa (ctg Leu	eptic .{142 gctgg ctc Leu	ie (2) gctag tgg Trp caa	ge ca get Val 15	cca Pro	stg see see see see see see see see see se	gag a Blu 7 Ecc Ser	aca g Thr 3 act Thr	gac s usp T ggt Gly 20	ca c hr I s act Thr	etc (eu l agt ser	tgt Cys	gga Gly	aat Aan 25	3
<2 <2 <4 gt 9 9 1 9 9 9	223 221 222 222 222 222 222 222 222 223	> De po	olype 08 25) caa (ctg Leu gta Val	eptic (142 ctq ctq ctq ctq Glu	is (2) (ctag tgg Trp caa Gin 30	grt Val 15 ggr Gly	eca Pro gaa glu	stg cler cler coly gaa Clu	tec Ser	act Thr gat Asp 35	ggt ggt 20	ca c	agt Ser	tgt Cys agr	gga gly gac Asp 40	aat Asn 25 cag	3
<pre>< < gt gt gt gt G G t £</pre>	223 220 221 222 220 220 231 233	> De po	olype olype os octa ctg leu gta Val	eptic (142 ctc ctc Leu gaa Glu	tgg Trp caa Gin 30	git git 15 ggr gly	cca Pro gsa glu	stg comet co	tee Ser Lgt Cys	act Thr gat Asp 35	gac s sp 1 ggt 20 tgt tgt	ca c	eu l agt Ser tat Tyr	tgt Cys agr agr	gga Gly gac Asp 40	trp aat Asn 25 cag Gln aaa	3
<pre>< < gt gt gt gt G G t £</pre>	223 220 221 222 220 220 231 233	> De po	olype olype os octa ctg leu gta Val	eptic (142 ctc ctc Leu gaa Glu	tgg Trp caa Gin 30	git git 15 ggr gly	cca Pro gsa glu	stg comet co	tee Ser Lgt Cys	act Thr gat Asp 35	gac s sp 1 ggt 20 tgt tgt	ca c	eu l agt Ser tat Tyr	tgt Cys agr agr	gga Gly gac Asp 40	trp aat Asn 25 cag Gln aaa	3
<pre></pre>	223 220 221 222 220 220 231 233	> De po	olype olype os octa ctg leu gta Val	eptic (142 ctc ctc Leu gaa Glu	tgg Trp caa Gin 30	git git 15 ggr gly	cca Pro gsa glu	stg comet co	tec Ser cgt Cys	act Thr gat Asp 35	gac s sp 1 ggt 20 tgt tgt	ca c	eu l agt Ser tat Tyr	tgt Cys agr agr gga Gly	gga Gly gac Asp 40	trp aat Asn 25 cag Gln aaa	3
<pre>< < gt gt gt gt G G t £</pre>	223 220 221 222 220 220 231 233	> De po	olype olype os octa ctg leu gta Val	ctc Leu gaa Glu	tgg Trp caa Gin 30	git git 15 ggr gly	cca Pro gsa glu	stg comet co	tee Ser Lgt Cys	act Thr gat Asp 35	gac s sp 1 ggt 20 tgt tgt	ca c	eu l agt Ser tat Tyr	tgt Cys agr agr	gga Gly gac Asp 40	trp aat Asn 25 cag Gln aaa	3
< <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 <2 </td <td>223 223 223 223 223 223 223 223 223</td> <td>> De po</td> <td>olypo olypo os os cta cta cta teu gts vai gar Asp</td> <td>eptic . {142 ctc Leu gaa Glu gaa Glu 45</td> <td>tgg trp caa gin 30 tgc</td> <td>get: get 15 ggt gly tgc Cys</td> <td>cca Pro gas Glu tte</td> <td>der Coly gaa Glu gat Asp</td> <td>tec Ser Lgt Cys gea 50</td> <td>act Thr gat Asp 35 aat</td> <td>ggt ggt ggt zo cys</td> <td>cca carrier sact Thr ggc Gly</td> <td>etc (eu l agt ser tat Tyr gag</td> <td>tgt Cys agt agt ser gga Gly 55</td> <td>gga gly gac Asp 40 aga Arg</td> <td>aat Asn 25 cag Gln aaa Lys</td> <td>3</td>	223 223 223 223 223 223 223 223 223	> De po	olypo olypo os os cta cta cta teu gts vai gar Asp	eptic . {142 ctc Leu gaa Glu gaa Glu 45	tgg trp caa gin 30 tgc	get: get 15 ggt gly tgc Cys	cca Pro gas Glu tte	der Coly gaa Glu gat Asp	tec Ser Lgt Cys gea 50	act Thr gat Asp 35 aat	ggt ggt ggt zo cys	cca carrier sact Thr ggc Gly	etc (eu l agt ser tat Tyr gag	tgt Cys agt agt ser gga Gly 55	gga gly gac Asp 40 aga Arg	aat Asn 25 cag Gln aaa Lys	3
<pre><f color="block"> <i colo<="" td=""><td>223 223 223 223 223 223 223 223</td><td>> De po</td><td>olypo olypo os ses ctg leu gts vai gar sap</td><td>ctc Leu gaa gGlu gsaa GGlu 45</td><td>tgg Trp caa Gin 30 tgc Cys</td><td>grt Val 15 15 ggr cly tgc Cys</td><td>cra Pro gaa Glu ttc Phe</td><td>der Cly gas Glu gat Asp</td><td>tee Ser tgt Cys</td><td>act Thr 7 act Thr gat Asp 35 aat Asn</td><td>ggt ggy 20 tgt Cys</td><td>ca canca can</td><td>etc (en l age Ser tat Tyr gag</td><td>tgt Cys agr agr gga Gly 55</td><td>gga gly gac Asp 40 aga Arg</td><td>aat Asn 25 cag Gln aaa Lys</td><td>3</td></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></f></pre>	223 223 223 223 223 223 223 223	> De po	olypo olypo os ses ctg leu gts vai gar sap	ctc Leu gaa gGlu gsaa GGlu 45	tgg Trp caa Gin 30 tgc Cys	grt Val 15 15 ggr cly tgc Cys	cra Pro gaa Glu ttc Phe	der Cly gas Glu gat Asp	tee Ser tgt Cys	act Thr 7 act Thr gat Asp 35 aat Asn	ggt ggy 20 tgt Cys	ca canca can	etc (en l age Ser tat Tyr gag	tgt Cys agr agr gga Gly 55	gga gly gac Asp 40 aga Arg	aat Asn 25 cag Gln aaa Lys	3
<pre><f color="block"> <i colo<="" td=""><td>223 223 223 223 223 223 223 223</td><td>> De po</td><td>olypo</td><td>ctc Leu gaa gGlu gsaa GGlu 45</td><td>tgg Trp caa Gin 30 tgc Cys</td><td>grt Val 15 15 ggr cly tgc Cys</td><td>cra Pro gaa Glu ttc Phe</td><td>stg set collection of the coll</td><td>tee Ser tgt Cys</td><td>act Thr 7 act Thr gat Asp 35 aat Asn</td><td>ggt ggy 20 tgt Cys</td><td>ca canca can</td><td>etc (en l age Ser tat Tyr gag</td><td>tgt Cys agt agt ser gga Gly 55</td><td>gga gly gac Asp 40 aga Arg</td><td>aat Asn 25 cag Gln aaa Lys</td><td>1</td></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></f></pre>	223 223 223 223 223 223 223 223	> De po	olypo	ctc Leu gaa gGlu gsaa GGlu 45	tgg Trp caa Gin 30 tgc Cys	grt Val 15 15 ggr cly tgc Cys	cra Pro gaa Glu ttc Phe	stg set collection of the coll	tee Ser tgt Cys	act Thr 7 act Thr gat Asp 35 aat Asn	ggt ggy 20 tgt Cys	ca canca can	etc (en l age Ser tat Tyr gag	tgt Cys agt agt ser gga Gly 55	gga gly gac Asp 40 aga Arg	aat Asn 25 cag Gln aaa Lys	1
<pre><f color="block"> <i colo<="" td=""><td>223 223 223 223 223 223 223 223</td><td>> De po</td><td>olypo olypo os ses ctg leu gts vai gar sap</td><td>ctc Leu gaa gGlu gsaa GGlu 45</td><td>tgg Trp caa Gin 30 tgc Cys</td><td>grt Val 15 15 ggr cly tgc Cys</td><td>cra Pro gaa Glu ttc Phe</td><td>der Cly gas Glu gat Asp</td><td>tee Ser tgt Cys</td><td>act Thr 7 act Thr gat Asp 35 aat Asn</td><td>ggt ggy 20 tgt Cys</td><td>ca canca can</td><td>etc (en l age Ser tat Tyr gag</td><td>tgt Cys agr agr gga Gly 55</td><td>gga gly gac Asp 40 aga Arg</td><td>aat Asn 25 cag Gln aaa Lys</td><td>1</td></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></f></pre>	223 223 223 223 223 223 223 223	> De po	olypo olypo os ses ctg leu gts vai gar sap	ctc Leu gaa gGlu gsaa GGlu 45	tgg Trp caa Gin 30 tgc Cys	grt Val 15 15 ggr cly tgc Cys	cra Pro gaa Glu ttc Phe	der Cly gas Glu gat Asp	tee Ser tgt Cys	act Thr 7 act Thr gat Asp 35 aat Asn	ggt ggy 20 tgt Cys	ca canca can	etc (en l age Ser tat Tyr gag	tgt Cys agr agr gga Gly 55	gga gly gac Asp 40 aga Arg	aat Asn 25 cag Gln aaa Lys	1
<pre><f color="block"> <i colo<="" td=""><td>223 223 223 223 223 223 223 223</td><td>> De po</td><td>olypo</td><td>ctc Leu gaa gGlu gsaa GGlu 45</td><td>tgg Trp caa Gin 30 tgc Cys</td><td>grt Val 15 15 ggr cly tgc Cys</td><td>cra Pro gaa Glu ttc Phe</td><td>stg set collection of the coll</td><td>tee Ser tgt Cys</td><td>act Thr 7 act Thr gat Asp 35 aat Asn</td><td>ggt ggy 20 tgt Cys</td><td>ca canca can</td><td>eu I agt ser tat Tyr gag Glu caa</td><td>tgt Cys agr agr gga Gly 55</td><td>gga gly gac Asp 40 aga Arg</td><td>aat Asn 25 cag Gln aaa Lys</td><td>1</td></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></i></f></pre>	223 223 223 223 223 223 223 223	> De po	olypo	ctc Leu gaa gGlu gsaa GGlu 45	tgg Trp caa Gin 30 tgc Cys	grt Val 15 15 ggr cly tgc Cys	cra Pro gaa Glu ttc Phe	stg set collection of the coll	tee Ser tgt Cys	act Thr 7 act Thr gat Asp 35 aat Asn	ggt ggy 20 tgt Cys	ca canca can	eu I agt ser tat Tyr gag Glu caa	tgt Cys agr agr gga Gly 55	gga gly gac Asp 40 aga Arg	aat Asn 25 cag Gln aaa Lys	1
st s	/s /s /s /s /s /s /s /s /s /s /s /s /s /	> De po	olypo	ctc Leu gaa Glu gsa Glu 45	tgg Trp caa Gin 30 tgc Cys	get carried ca	oca Pro gsa Glu tte Phe assa Lys	det constant of the constant o	tec Ser Cys gea Ala 50 tgc Cys	act for act fo	ggt gly 20 tgt Cys cas Gin ccs Pro	ca carrier I s act Thr ggc Gly	agt ser tat tyr gag Glu caa Gln 70	tgt Cys agr agr gga Gly 55	gga gly gac Asp 40 aga Arg	aat Asn 25 Cag Gln aaa Lys tgt Cys	5 9 1 1 1 2 2
44 gt 9 gt 1 gt 2	223 220 222 222 222 222 222 222 222 222	> Depo po p	olype olype olype ctg leu gta Val gar asp ctg leu 60	ctc Leu gaa Glu gaa Lys cag	tgg trp caa Gin 30 tgc Cys	gett Val 15 9gt Gly tgc Cys 99g Gly	cra Pro gsa glu tte phe	det gest gest gest gest gest gest gest ge	tec Ser Lgt Cys gea Ala 50 tgc Cys	act Thr gat Asp 35 aat Asn agt Ser	ggt ggy 20 tgt Cys Cas Gin	cca cance in the second	agt ser tat Tyr gag Glu caa Gln 70	tgt Cys agr ser gga Gly 55 ggt Gly	gga Gly gac Asp 40 aga Arg	aat Asn 25 cag Gln aaa Lys tgt Cys	3
44 gt	223 220 222 222 222 222 222 222 222 222	> Depo po p	olype olype olype ctg leu gta Val gar asp ctg leu 60	ctc Leu gaa Glu gaa Lys cag	tgg trp caa Gin 30 tgc Cys	gett Val 15 9gt Gly tgc Cys 99g Gly	cra Pro gsa glu tte phe	det gest gest gest gest gest gest gest ge	tec Ser Lgt Cys gea Ala 50 tgc Cys	act Thr gat Asp 35 aat Asn agt Ser	ggt ggy 20 tgt Cys cas Gin	cca cance in the second	agt ser tat Tyr gag Glu caa Gln 70	tgt Cys agr agr gga Gly 55	gga Gly gac Asp 40 aga Arg	aat Asn 25 cag Gln aaa Lys tgt Cys	3

1																gct Ala		339
The filn val Cys Ile Asn Gly Gln Cys Ala Gly Ser Ile Cys Glu Lys 115 115 116 115 115 116 115 115 116 115 115	S	tge Cys	eca	gca	tet	Asp	cct	aaa Lys	cca Pro	aac Asn	Phe	aca	gac Asp	tgt Cys	aat Asn	Arg	cat His	387
Tyr Gly Leu Glu Glu Cys Thr Cys ala Ser Ser Asp Gly Lys Asp Asp Asp 140 Raa gas tts tgc cat gts tgc tgt atg asg ass atg gac cca tca act Lys Glu Leu Cys Hin Val Cys Cys Met Lys Lys Met Asp Pro Ser Thr 155 156 157 158 159 159 159 159 159 159 159	10	aca Thr	caa Gln	gtg Val	Cys	att	aat Asn	gjà 333	Caa Gln	Cys	gca Ala	ggt	tet Ser	atc Ile	Cys	gag Glu	aaa Lys	435
Ly8 Glu Leu Cy8 Hin Val Cy8 Cy8 Met Ly8 Ly8 Met Amp Pro Ser Thr 155 165	16			Leu	Glu				Cys					Gly				433
Cys Ala Ser Thr Gly Ser Val Gln Trp Ser Arg His Phe Ser Gly Arg 170 acc atc acc ctg cas cct sgs toc ctt tgc aac gat tt ags ggt cag 28 Thr 11s Thr Leu Gln Pro Gly Ser Pro Cys Ann Asp Phe Arg Gly Tyr 180 200 tgt gat gtt ttc atg egg tgc sgs tta ggt get get get ggt cct ct 200 gct ags tgt ttc atg egg tgc sgs tta ggt gct sgt ggt cct ct 200 gct ags tgt ttc atg egg tgc sgs tta ggt gct ggt ggt cct ct 200 gct agg tgt ttc atg egg tgc sgs tta ggt gct ggt ggt cct ct 200 gct agg tgt ttc atg egg tgc sgs tta ggt gct ggt ggt cct atg 200 gct agg tgt ttc atg egg tgc sgs tta gtc gct ggt ggt cct atg 200 gct agg tgt tgc sgs tta fac cca gag ccc tst gga anc att Ala Arg Leu Lys Lys Ala Ile Phe Ser Pro Glu Leu Tyr Glu Asn Ile 210 220 gct gaa aga tct tgt gac asa act cac aca tgc cca cg tgc cca gca Ala Glu Arg Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala 215 cct gaa gcc gag ggg egg ccg tca gtc ttc ctc ttc ccc cca aaa ccc 216 aag gac acc ctc atg atc tcc egg acc cct gag gtc aca tgc gtg gtg 275 286 gtg gac gtg agc cac gas gac cct gag gtc aac ttc gg tac gtg 276 gtg gac gtg agc cac gas gac cct gag gtc aac ttc gg tac gtg 277 287 gtg gac gtg agc cac gas gac cct gag gtc aac ttc gg gag gag cag 287 40 gtg gac gtg agc cac gas gac cct gag gtc aac ttc gg acc cct gag gtc acc tgg gag gag cag 277 287 gtg gac gtg agc cac gas gac cct gag gtc aac ccg gag gag gac gag 287 40 gac ggc gtg gag gtg cat aat gcc aag aca aaa gcc gcg gag gag cag 287 298 299 295 296 gac ggc gtg gag gtg cat aat gcc aag aca aaa gcc gcg gag gag cag 295 295 296 297 297 298 299 309 295 296 297 297 297 297 298 299 295 296 297 297 297 297 298 299 295 296 297 297 298 297 297 298 299 299		aaa Lys	Glu	tta	cys	His	gra Val	Cys	tgt Cys	atg Met	aag Lys	Lys	Met	gac Asp	Pro	tca Ser	act Thr	531
### The The Use Offen Pro City Sen Pro Cys Aman Asp Phe Arg Gily Tyx 190	30	CAs	gcc Ala	agt 8er	Thr	999 Gly	Ser	gtg Val	cag Gln	tgg Trp	agt. Ser	Arg	cac His	tte Phe	agt Ser	ggt Gly	Arg	579
Cys Asp Val Phe Net Arg Cys Arg Leu Val Asp Als Asp Gly Pro Leu 215	25	acc	atc	acc	ctg Leu	Gln	Pro	gga Gly	toc Ser	cct Pro	Cys	aac Asn	gat Asp	t.t.t. Phe	aga Arg	Gly	tac Tyr	627
Ala Arg Leu Lys Lys Ala Ile Phe Ser Pro Glu Leu Tyr Glu Asn Ile 225 225 225 275 275 286 287 288 298 299 299 299 299 209 100 100 100 100 100 100 100 100 100 1	30	tgt Cys	gat Asp	gtt Val	Phe	atg Met	egg	tga Cys	aga Arg	Leu	gta Val	gat	get Ala	gat Asp	Gly	cct Pro	cta Leu	675
Ala Giu Arg Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala 245 cet gas gec gag geg eeg eeg tea gte tte ette eee eea aaa eec 819 Pro Giu Ala Giu Giy Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro 265 aag gac acc etc atg atc tee egg acc eet gag gte aca tge gig gtg 265 aag gac acc etc atg atc tee egg acc eet gag gte aca tge gig gtg 270 275 286 ggg gac gtg agc cac gas gac eet gag gte aag te aac teg gtg gtg 270 287 287 486 ggg gac gtg agc cac gas gac eet gag gte aag te aac teg gte gtg 270 288 487 ggg gac gtg agc cac gas gac eet gag gte aag te aac teg gte gtg 275 289 580 gac ggc gtg gag gtg eat aat goc aag aca aag eeg egg gag gag eag eag 289 Asp Giy Val Giu Val His Aan Ala Lys Thr Lys Pro Arg Giu		ger. Ala	agg Arg	Len	Lys	aaa Lys	gca Ala	att Ile	Phe	agt Ser	cca Pro	gag Glu	ctc Leu	Tyr	gaa Glu	aac Asu	att Ile	723
Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro 250 255 255 266 265	35	got Ala	Glu	aga Arg	tet	tgt Cys	gac Asp	Lys	act Thr	cac His	aca Thr	cys	Pro	ecg Pro	tgc Cys	oca Pro	gca Ala	771
Lys Asp Thr Leu Net Ile Ser Arg Thr Pro Oli Val thr Cyr Val Val 220 270 280 280 280 280 280 280 280 280 280 28	40	Pro	gaa Glu	Ala	gag Glu	ggc Gly	Ala	ccg Pro	tca Ser	gtc Val	tto Phe	Lea	ttc Phe	Pro	cca Pro	aaa Lys	Pro	819
gig gac gig age cac gas gac cet gag gic aag the aac tog tac gig yal Asp Val Ser His olu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val 295 50 gac ggc gig gag gig cat aat goc aag aca aag ceg egg gag gag cag Asp Oly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Clu Clu Clu Clu Clu Clu Clu Clu Clu C	45					Met					Pro					Val		867
Amp Gly Wal Glu Wal His Amn Ala Lys Thr Lys Pro Arg Glu Glu Glu Glu 100 tac sac agc acg tac cgg gtg gtc agc gtc cc acc gtc crg cac cag 1011 55 Tyr Amn Sex Thr Tyr Arg Wal Wal Ser Wal Leu Thr Wal Leu His Glu		gtg Val	gac Asp	gtg Val	Ser	cac	gaa Glu	gac Asp	ect Pro	Glu	gtc Val	aag Lys	tta Phe	aac Asn	Trp	tac Tyr	gtg Val	915
1011 Tyr Asn Sex Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln	50	gac Asp	ggc	Val	gag Glu	gtg Val	cat His	aat Asn	Ala	aag Lys	aca Thr	aag Lys	ccg Pro	Arg	gag Glu	gaq Glu	cag Gln	963
		1011	i.															
	56	Tyr	Asn 315	Ser	The	Tyr	Arg	Val 320	Val	Ser	Val	Leu		val	Leu	His	Gln	

	gac tgg ctg aat g	gc aag	gag tac	aag tgc	aag gt	e tec	аас ава	gce
	1059	13 x 7 x x x	77. m	T				
5	Asp Trp Leu Asn 6	335	GIU TYF	mys cys	340	L Ser.	asn Lys	34
	ete oca gee eee a	tc gag	aaa acc	ato toc	aaa ge	aaa :	ggg cag	ca
	Leu Pro Ala Pro I	le Glu	Lys Thr	Ile Ser	Lys Ala	lys :	Gly Gln 360	
10								
	cga gaa cca ca g g 1155	rg tac	acc ctg	ece cea	tec egg	g gat	gag ctg	ace
15	Arg Glu Pro Gln V 365	al Tyr	Thr Leu	Pro Pro 370	Ser Ar		Glu Leu 375	Th
	aag aac cag gtc a	ge etg	acc tgc	ctg gtc	aaa gg	tto	tat ecc	age
	Lys Asn Gln Val S	er Leu	Thr Cys 385	Leu Val	Lys Gly	7 Phe 390	Tyr Pro	Se:
80	gac atc gcc gtg g	jag tgg :		aat ggg	cag cc		aac aac	ta
	1251 Asp Ile Ala Val G 395		Glu Ser	Asn Gly	Gin Pro		Asn Asn	Ty
25	372		400		403	•		
as	aag acc acg cct c 1299							
	Lys Thr Thr Pro F	ro Val:	Leu Asp	Ser Asp	Gly Ser 420	r Phe	Phe Leu	17y
90	age and etc mee g	ftg gac	aag ago	agg tgg	cag cag	999	aac gto	tt
	Ser Lys Lea Thr V	al Amp	bys Ser	Arg Trp 435	Gln Gli	Gly	Asn Val 440	
35	tea tgo teo gtg a	itg cat	gag get	ctg cac	aac cas	rac.	acg cag	a.a.
	Ser Cys Ser Val M	let His (Glu Ala	Leu His 450	Asn His		Thr Gln 455	Ly
	ago oto tee otg t	et eeg	ggt sas	tga act	agagegg	acgat.	acaga t	
40	1443 Ser Leu Ser Leu S 460	er Pro	Gly Lys 465					
45	<210> 6							
	<211> 465 <212> PRT <213> Artificial	Sequence	e					
	<220>							
50	<223> Description polypeptide		ificial	Sequence	e: fusio	m		
	<400> 6							
			* ***					_
56	Met Glu Thr Asp T	hr Leu :	Leu Leu	Trp Val	Leu Lei	i Leu	Trp Val	

Glu Cys Asp Cys Gly Tyr Ser Asp Gln Cys Lys Asp Glu Cys Cys Phe 35 40 45 Asp Ala Asn Gln Pro Glu Gly Arg Lys Cys Lys Leu Lys Pro Gly Lys Gln Cys Ser Pro Ser Gln Gly Pro Cys Cys Thr Ala Gln Cys Ala Phe Lys Ser Lys Ser Glu Lys Cys Arg Asp Asp Ser Asp Cys Ala Arg Glu Gly lie Cys Asn Gly Phe Thr Ala Leu Cys Pro Ala Ser Asp Pro Lys Pro Asn Phe Thr Asp Cys Asn Arg His Thr Gln Val Cys Ile Asn Gly Gln Cys Ala Gly Ser Ile Cys Glu Lys Tyr Gly Leu Glu Glu Cys Thr 130 140 Cys Ala Ser Ser Asp Gly Lys Asp Asp Lys Glu Leu Cys His Val Cys Cys Not Lys Lys Met Asp Pro Ser Thr Cys Ala Ser Thr Gly Ser Val Gin Trp Ser Arg His Phe Ser Gly Arg Thr Ile Thr Leu Gin Pro Gly 3.80 Ser Pro Cys Asn Asp Phe Arg Gly Tyr Cys Asp Val Phe Met Arg Cys Arg Leu Val Asp Ala Asp Oly Pro Leu Ala Arg Leu Lys Lys Ala Ile Phe Ser Pro Glu Leu Tyr Glu Asn Ile Ala Glu Arg Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Als Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp 275 280 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn 290 295 300 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser bys Ala bys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 390 395 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 405 410 415 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu 440 445 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lvs

<210> 7

		1 > 1 2 > D															
			rtif	icia	1. Se	quen.	ce										
5	<22	0>															
	<22		escr olyp			f Ar	tifi	cial	Seq	uenc	e: f	usio	n				
	c22																
10		1> C	DS 41).	17.													
	482	22 (exj.	- 170	09)												
		0> 7															
18	cgg	gcee	cce ·	ctog	gäät.	dg a	ccca	agct	d ac	tage	cacc					aca Thr 5	55
	cto	otg	cta	tgg	gta	ctg	ctq	ctc	tag	qtt	cca	gat	tcc	act	aat.	ach	103
	Leu	Leu	Leu	Trp	Val 10	Leu	Leu	Leu	Trp	Val 15	Pro	Gly	Ser	Thr	61y 20	Thr	
20	201	ton	CONTR	224	***		ata				gag						
	Ser	Cys	Gly	Asn 25	Met	Phe	Val	Glu	Pro 30	GJA	Glu	Gln	Cys	Asp 35	Cys	Gly	151
25	rtc Phe	ctg	gat Asp 40	Asp	tgo	gtc Val	gat Asp	Pro 45	tge Cys	tgt Cys	gat Asp	tet Ser	ttg Leu 50	ace Thr	tgc Cys	cag Gln	199
.90											gga Gly						247
	tgc Cys 70	cag	Leu	cgc Arg	ecg Pro	tet Ser 75	Gly	tgg Trp	Cag	tgt Cys	agt Arg 80	ect Pro	acc Thr	aga Arg	gly 999	gat . Asp 85	295
36	tgt Cys	yab	ttg Leu	Pro	98a Glu 90	ttc Phe	tgc Cys	Pro	gjå	gac Asp 95	ser	tcc Ser	cag Gln	tgt Cys	ecc Pro 100	pro	343
40	gat Asp	gtc Val	agc Ser	cta Leu 105	999 Gl.y	gat Asp	ggc Gly	gag Glu	pro 110	tgc Cys	gct Ala	ggc	gly ggg	caa Gln 115	gct Ala	gtg Val	391
45	tge Cys	atg Met	cac His 120	ggg ggg	egt Arg	tgt Cys	gcc Ala	tec Ser 125	tat	gcc Ala	cag Gln	cag Gln	tgc Cys 130	cag Gln	tca Ser	ctt Leu	439
	tgg Trp	gga Gly 135	PTO	gga Gly	gcc Ala	cag Gln	ecc Pro 140	gct Ala	gcg	cca Pro	ctt Leu	tge Cys 145	ctc	cag Gln	aca Thr	get Ala	487
80	ast Asn 150	act	cgg Arg	gga	aat Asn	gct Ala 155	trt Phe	999 Gly	agc Ser	tgt Cys	999 Gly 160	ege Arg	aac Asn	ccc Pro	agt Ser	990 61y 165	535
85	agt Ser	car Tyr	grg Val	tcc Ser	tgc Cys 170	acc Thr	ect Pro	aga Arg	gat Asp	gcc Ala 175	att	tgt Cys	617 999	cag Gln	ete Leu 190	cag Gln	593

				99t Gly 185													631
5				aca Thr													679
10				gac Asp													727
18				gcc Ala													775
				gat													823
20				gtc Val 265													871
25				Pro													919
				aaa Lys													967
30	101	5		ccg		-									-		
	310	era	Ala	Pro	ser	315	Phe	Lex	Phe	Fro	320	Lys	9x0	Lys	Asp	325	
36	106	3		tcc													
	Leu	Met.	Ile	Ser	Arg 330	Thr	Pro	Glu	Val	Thr 335	Сув	Val	Val	Val	Asp 340	Val	
40	111	I		980													
	Ser	His	Glu	Asp 345	Pro	Glu	Val	Lys	Phe 350	asn	Trp	Tyr	Val	355	Gly	val	
45	115	9		aat													
	Ølu	Val	His 360	Asn	Ala	Lys	Thr	Lys 365	Pro	Arg	Glu	Glu	Gln 370	Tyr	Asn	Ser	
	acg 120		egt	gtg	gtc	agc	gte	ctc	acc	gtc	ctg	cac	cag	gac	tgg	ctg	
50	Thr	Tyr 375	Arg	Val	Val	Ser	Val 380	Leu	Thr	Val	Leu	His 385	Gln	Asp	Trp	Leu	
	125		aag	gag	tac	aag	tge	aag	gre	tcc	aac	aaa	gcc	cte	cea	gec	
86	Asn 390		Lys	Glu	Tyr	Lys 395	Çys	Lys	Val	Ser	Asn 400	Lys	Ala	Leu	Pro	Ala 405	

	00C 1303	ato	gag	aaa	acc	atc	rec	ааа	gee	aaa	999	cag	ccc	cga	gaa	cca
_	Pro	Tle	Glu	Lys	Thr	He	Ser	Lys	Ala	Lys 415	Gly	Gln	Pro	arg	Glu 420	Pro
5																
	Ca9 1351															
10	Gln	Val	Tyr	Thr 425	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Net	Thr	Lys 435	Asn	Gla
20	gt.c	arre	mina	arre	For	ata	ere		coa	* * * *			200			-
	1399															-
	Val	ser	440	Thr	Cys	Leu	Val	Lys 445	Gly	Phe	Tyr	Pro	Sex 450	qsA	Ile	Ala
1.5																
	gtg 1447		rgg	gag	agc	aat	999	cag	ccā	gag	aac	aac	Eac	aag	acc	ಷರದ್ವ
	Val	Glu 455	Trp	Glu	Ser	Asn	Gly 460	Gln	Pro	Glu	Asn	Asn 465	Tyr	Lys	Thr	Thr
20	cct	ccc	gtg	ctg	gac	tec	gac	qqc	tcc	tte	tte	ctc	tat	age	aac	ete
	1,495															
	Pro 470	Pro	Vai	Leu	Asp	475	qas	già	ser	Phe	Phe 480	Leu	Tyr	Ser	Lys	Leu 485
25	acc 1543		gac	aag	agc	agg	tgg	cag	cag	999	aac	gtc	ttc	tca	tge	tac
	Thr	Val	Asp	Lys	Ser 490	Arg	Trp	Gln	Gln	Gly 495	Asn	Val	Phe	Ser	Cys 500	Ser
	es bear	250	nat	~~~	onis	m to ex										
30	9tg 1591															
	Val	Met	His	G14 505	Ala	Leu	His	Asn	His 510	Tyr	Thr	Gln	PAs	Ser 515	Leu	Ser
35	ctg 1638	tot	ceg	ggt	aaa	tga	act	agaga	gg o	rege	acc	go go	gtgga	iget		
an .	Leu		Pro 520	gly	Lys											
ai)	<210 <211		10													
	<232															
	<23.3			cíal	L Sec	pueno	:e									
	<220															
45	<223			iptic eptic		Art	ific	cial	Sequ	ence	:: ft	sion	1			
	<400	> 8														
	Met		Thr	Asp	Thr	Leu	Leu	Leu	Trp		Leu	Leu	Leu	Trp		Pro
30	Gly:	Ser	Thr	Gly	The	Ser	Cvs	Gly	Asn	10 Met	Phe	Val	Glu	Pro	15 G1v	Gin
	Gln			28					25					30		
			35					40					45			
55	Ser .	50					55					60				
	Pro	Cys	Сув	Gln	Asn	CAs	Gln	Leu	Arg	Pro	Ser	Gly	Trp	Gln	Cys	Arg

		65					70										
			Thr	Arg	Gly	Asp 85		Asp	Leu	Pro	Glu 90	75 Pbe	Сув	Pro	Gly	Asp 95	80 Ser
5					1.00					Leu 105	Gly				110	Сув	
				115					120					125			
			130					135		Gly			148				
10		245					150			Gly		155					160
						165				Ser	170					175	
18					180					Gly 185					190		
				195					308	The				205			
			210					215		Asp Ala			220				
20		225					230			Asp		235					340
						245				Val	250					255	-
25					260					265 Pro					270		-
200			Thr	275				Cys	280	ьув				285			
			290 Ala	Pro	Glu	Ala		Gly	Ala	Pro	Ser-		300 Phe		Phe	Pro	
30		lys Lys	Pro	Lys	Aap	Thr 325	310 Leu	Met	Tle	ser		315 The	Pro	Glu	val		320 Cys
	1	/al	Val	Val.	Asp 340		Ser	His	Glu	Asp 345	330 Pro	Glu	Val	Lys	Phe 350	335 Asn	Trp
	3	lyr	Val	Asp 355		Val.	Glu	Val	His 360	Asn	Ala	Lys	Thr	Lys 365		Arg	Glu
36			370					375		Val			380	Leu			
	3	385					390			Glu		395					400
40						405				Lys	410					415	
					420					Thr 425					430		
				435					440	Thr Glu				445			
45			450					455		Leu			460				
	4	65					470			Lys		475					480
50						485				Glu	490					495	
au				Ser	500				Pro	505 Gly				- 11345	510	-3-	-412
				515					520								

<210> 9 <211> 1386

	<212> DNA <213> Artificial Sequence
8	<220> <223> Description of Artificial Sequence: fusion polypeptide
10	<2205 <2215 CDS <2225 (23)(1365)
	<400> 5 gtcgaccoma gctggctago caco atg gag aca gac aca ctc ctg cta tgg S1 Net Glu Thr Amp Thr Leu Leu Trp
15	1 5
	gta etg etg etc tgg gtt cca egt tcc act ggt act agt tgt ggg aac 99 Val Leu Leu Leu Trp Val Fro Gly Ser Thr Gly Thr Ser Cys Gly Asn 10 25
20	tog agg gkg gat gaa ggm gaa gog tgt gat cet ggc atc atg tat etg 147 Ser arg Val aap Glu Gly Glu Glu Cya aap Pro Gly Ile Met Tyr Leu 3 40
25	asc sac gac acc tgc tgc sac agc gac tgc acg ttg sag gas ggt gtc 195 han Asm Aup Thr Cys Cyx han Ser Acp Cyu Thr Leu Lys Glu Gly Val 50 45
	cas tgc agt gac agg aac agt oot tgc tgt aaa aac tgt cag ttt gag 243 Gln Cys Ser Amp Arg Asn Ser Pro Cys Cys Lys Aan Cys Gln Phe Glu 60 60 60
362	act gee cag aag aag tge cag gag geg att aat get act tge aaa gge 291 Thr Ala Gln Lys Lys Cys Gln Glu Ala Ile Asn Ala Thr Cys Lys Gly 75 80 85
36	gig tor tac tgc sca ggt sat agc agt gag tgc ccg cct cca gga aat 339 Val Ser Tyr Cys Thr Cly Ams Ser Ser Glu Cys Pro Pro Pro Cly Amn 90 105
40	get gas gat gac act git tge ttg gat ett gge aag tgt aag gat ggg 387 Ala Glu Asp Asp Thr Val Cys Leu Asp beu Gly Lya Cys Lya Asp Gly 110 120
	asa tgo ato cot the tgo gag agg gas cag cag cag sag too tgt goa 435 Lyo Cys lle Pro Phe Cys Olu Arg Olu Gin Gin Leu Glu Ser cys Ala 125
45	tgE akt gas act gac aad too tge eag gtg tgc tgc agg gac ctt too Cys hen Glu Thr Asp Amn Ser Cys Lys Val Cys Cys Arg Asp Leu Ser 140 145 150
50	ggc cgc tgt gtg coc tat gtc gat gct gaa caa aag dac tta ttt ttg Gly Arg Cys Val Pro Tyr Val Rep Ala Clu Gin Lys Ren Leu Phe Leu 155
	agg aas gga sag coc tgt acs gta gga ttt tgt gac atg aat ggc aaa 279 Arg Lys Cly Lys Pro Cys Thr Val Gly Phe Cys Asp Met Asn Cly Lys 170 180 185
56	tgt gag aaa oga gta oag gat gta att gaa oga ttt tgg gat tto att 627

	Cys	Glu	Lys	Arg	Val. 190	Gln	Asp	Val	Ile	Glu 195	Arg	Phe	Trp	Asp	Phe 200	Ile	
5		~~~	ends en	0.00													
	QEA	Gln	Leu	Ser 205	ile	Asn	Thr	Phe	99a Gly 210	Lys	Phe	Leu	Ala	Asp 215	Asn	aga Arg	675
	ton	hat	mac	252	act	cac	201	raa	cerc a	000	haa	(3)7 3	***	ont	~~~		723
1(7	Ser	Cys	Asp 220	Lys	Thr	His	The	Cys 225	Pro	Pro	Cys	Pro	Ala 230	Pro	Glu	Ala	743
	gag Glu																771
15																	
	ste Leu 250	atg Met	Ile	Ser	arg arg	Thr 255	Pro	gag Glu	gtc Val	aca	tge Cys 260	gtg Val	gtg Val	gtg Val	gac	gtg Val 265	819
	200	~~~	~~~	000	eren ke								-			- 5- 5-	
20	age Ser	His	Glu	Asp	Pro 270	Glu	Val	ràs	Phe	Asn 275	Trp	Tyr	Val	yeb	Gly 280	Val	867
	gag	gtg	cat	aat	gee	aag	aca	aag	ceg	cgg	gag	gag	cag	tac	anc	agc	915
25	Glu '	Val	His	Asn 285	Ala	Lys	Thr	liye	Pro 290	Arg	Glu	Glu	Gln	Tyr 295	Asu	ser	
	acg Thr	tac Tyr	ogg Arg 300	gtg Val	gtc Val	agc Ser	gt <i>c</i> Val	ctc Leu 305	Thr	gtc Val	ctg Leu	cac His	cag Gln 310	gac Asp	tgg Trp	ctg Leu	963
30	aat :																
	Asn:	Gly 315	Lys	Glu	Tyr	Lys	350 CAs	Lys	Val.	Ser	Asn	Lys 325	Ala	Leu	Pro	Ala	
.35	1059																
	330	116	214	туу	LIIL	335	251	nys	ATA	гÀя	340 340	GIR	Pro	arg	GIU	345	
40	cag :	gtg	tec	acc	ctg	ccc	cca	tee	cgg	gat	gag	ctg	acc	aag	aac	cag	
	Gln	Val.	Tyr	Thr	Leu 350	Pro	Pro	Ser	Arg	Asp 355	Glu	Leu	Thr	Lys	Asn 360	Gln	
	gte :	agc	etg	acc	tge	ctg	gtc	aaa	ggc	ptc	tat	ecc	age	gac	ate	gcc	
45	1195 Val	Ser	Leu	Thr 365	Сув	Leu	Val	Lys	Gly 370	Phe	Tyr	Pro	Ser	Asp 375	Ile	Ala	
	gtg :	gag	tgg	gag	agc	aat	999	cag	ccg	gag	aac	aac	tac	aag	acc	acg	
52	Val	Glu	Trp 380	Glu	Ser	Asn	Gly	Gln 385	Pro	Glu	Asn	Asn	Tyr 390	Lys	Thr	Thr	
	1251	ccc	gtg	ctg	gac	tcc	gac	ggc	tee	ttc	ttc	ote	tac	agc	aag	cte	
55	Pro	95 395	Val	Leu	Asp	Ser	Asp 400	Gly	Ser	Phe	Phe	Ъец 405	Tyr	Ser	Lys	Leu	

	acc g	tg gac	aag	agc	agg	tgg	cag	cag	999	aac	gt.c	tto	tca	tgc	tice	
	3299															
	Thr V	dsy te	bys	Ser	Arg	Trp	Gln	Gla	Gly		Val	Phe	Ser	CAa		
5	419				415					420					425	
				and the		- 1										
	919 a	tg cat	gag	get	ceg	cac	aac	cac	tac	acg	cag	aag	age	ctc	ccc	
	7341															
	Val M	et Ris	Glu	A3 a	Lest	Sis	Asp	Ris	Tur	The	Gla	T.ven	Ser	T.0013	Cor	
10				430					435		~~	wy	CCX	440	2000	
	ctg t	et eeg	ggt	aaa	tga	acti	agage	rgg (ecgel	aca	ga t					
	1386															
	Leu S	er Pro		Lys												
15			445													
,,																
	4020.	3.0														
		<210> 10 <211> 446														
	<212>															
20			icia	. Sec	men	ce										
20	<213> Artificial Sequence															
	<220×															
	<223>	Descr:	iptic	on o	E Ar	tifi	cial	Seq	ience	9: D	sion	1				
		polype	ept1	îe												
25	<400>															
~~			2	mb	7	*	Y	m	174.3							
	nec s	lu Thr	day	rnr	ren	ren	ren	Erp	1D	ran	ren	ren	Trp		Pro	
	01v 8	er Thr	alv	Thr	Ser	Cva	G) v	hen		2	Um 3	A aw	<i>a</i> 3 <i>v</i>	25	C1	
	/		20	****	M.O.	-,0	U.L.	25	004	west	Year	nay	30	GLy	outu	
30	Glu C	ys Asp	Pro	Gly	Ile	Met	Tyr		Ass	Asn	Asp	Thr		Cvs	Asn	
		35					40					45				
		ар Сув	Thr	Leu	Lys	Glu	Gly	Val	Gln	Сув	Ser	Asp	Arg	Asn	Ser	
		50				55					60					
	Pro C	ys Cys	rys	Asn		Gln	Phe	G] u	Thr		Gln	FÀS	Lys	Cys		
35	65				70		_			75					80	
3.0	GIII A	la Ile	ASD	85	rnr	Cys	Lys	gtA		Ser	TYT	CAs	Thr		Asn	
	Ser S	er Glu	CVR		pro	arn	G3 11	Aum	90	a) v	ran	N nm	The	95	Ch 10	
		01 014	100			110	GIY	105	27.7.07	GIG	weith	Asp	110	0.60.7	Chs	
	Leu A	sp Leu		Lvs	Cvs	Lvs	Asp		INS	CVs	Tie	pro		Cvs	Glo	
40		115			-		120	,		-2-		1.25		-,-		
	Arg G	lu Gln	Gln	Len	Gla	Ser	Cys	Ala	Cys	Asn	Glu	Thr	Asp	asn	Ser	
	1	30				3.35					140					
	Cya L	ys Val	Сув	Суя		Asp	ren	Ser	gly		Cys	Val	Fro	Tyr		
	145	2 - 72	m2	*	150	*	n			155			_	_	160	
45	wah w	la Glu	G.1.31	165	Asu	ren	ene	rea	170	Lys	GIA	rva	Fro	175	TAX	
	Val G	ly Phe	Cure		Met	Zen.	e) w	Tare		a3.,	T.+00+	A 100	11~3		Xain	
		-2	180	, m., p	7 142 0		v.,	185	~ya	914	wys	571.53	196	0141	ray	
	Val I	le Glu	Arg	Phe	Trp	Asp	Phe		Asp	Gln	Leu	Ser		Asn	Thr	
		3.95					200					205				
50	Phe G	ly Lys	Phe	Leu	Ala	qaA	Asn	Arg	ser	Cys	Asp	Lys	Thr	His	Thr	
	2	10				215					220					
		ro Pro	Cys	Pro		Pro	Glu	Ala	Glu		Ala	Pro	Ser	Val		
	225			T	230	*			_	235					240	
	ren 5	he Pro	PEO	245	Pro	ьyз	asp	Thr		Met	Lie	ser	Arg		Pro	
55	Glu 9	al Thr	Cun		Va3	Yes	ă en	1/47	250	ui e	m1	her	time	255	15-2	
	ozu v	4144	260	J tail	read	< 66.1	wass	265	DOT.	4113	sea ti	stat.	270	OIS	ANT	
								~~~					~, 0			

	Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr 275 280 285														
	Lys Pro Arg Glu Glu Glu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val 295 308														
5	Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys														
	Lys Val Ser Asn Lys Ala Leu Pro Ala Pro ile Glu Lys Thr Ile Ser														
10	325 330 335 Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Len Pro Pro														
10	340 345 350 Ser Arg Asp Glu beu Thr Lys Asp Glu Val Ser Leu Thr Cys Leu Val														
	355 360 365 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asp Gly														
	370 375 380 Gln Pro Glu Asn Asa Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp														
15	385 390 395 400														
	Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp 405 410 415														
	Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His														
20	Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys														
	435 440 445														
	<210> 11														
25	<211> 1653														
	<212> DNA <213> Artificial Sequence														
	<220>														
	<223> Description of Artificial Sequence: fusion														
90	polypaptide														
	<220»														
	<221> CDS <222> (25)(1632)														
35	<400> 11														
	gtegacecaa getggetage cace atg gag aca gac aca etc etg eta tgg 5: Net Glu Thx Asp Thr Leu Leu Trp														
	1 5														
40	gts ofg ofg off tog gft oca ggt too act ggt sot agt tgt ggg ast g														
	Val Leu Leu Eur Trp Val Pro Gly Ser Thr Gly Thr Ser Cys Gly Asn 10 15 20 25														
	cta gig git gas gas ggg gag gas igt gas igt gga acc ata cgg cag 1:														
45	Leu Val Val Glu Glu Gly Glu Glu Cys Asp Cys Gly Thr Ile Arg Gln														
	THE WAY THE OUT THE PART AND THE														
	tgs goa aaa gat coo tgt tgt otg tta aad tgt act cta cat cot ggg 19 Cys Ala Lys Asp Pro Cys Cys Leu Leu Asn Cys Thr Leu His Pro Cly														
80															
	get get igt get itt gga ata igt ige aaa gae ige aaa itt eig eea 20 Ala Ala Cys Ala Phe Gly Ile Cys Cys Lys Asp Cys Lys Phe Leu Pro														
	60 65 70														
	toa gga act tta tgt aga cae caa gtt ggt gaa tgt gac ctt cca gag 25														
95	Ser Gly Tar Leu Cys Arg Gln Gln Val Gly Glu Cys Asp Leu Pro Glu 75 80 85														

	Trp			999 Gly		Ser					Asp					Gln	339
5	90					95					100					105	
	Asp			Sex													387
io	aat Asn	aac Asn	Cat His	gat Asp 125	ata	caa Gln	tgt Cys	aaa Lys	9ag Glu 130	att Ile	ttt Phe	ggc Gly	caa Gln	gat Asp 135	gca Ala	agg Arg	435
18	agt Ser	gca Ala	tot Ser	cag Gln	agt Ser	tge Cys	tac Tyr	caa Gln 145	gas Glu	atc Ile	aac Asn	ace	caa Gln 150	gga Gly	aac Asn	egt Arg	483
				tgt Cys				ggc					äää				531
843	pot	gat	atc	atg	tgt	333	agg	gtt	cag	tgt	gaa	aat	gtg	gga	gta	att	579
	270 170	Asp	Lle	Net	cys	G1y 175	yrg	Val	Gln	Cys	Glu 180	Asn	Val	Gly	Val	lle 185	
es	pro	aat	Leu	ata	gag Glu 190	His	tct Ser	aca	gtg Val	Gln 195	cag Gln	ttt Phe	CAC His	ctc Leu	aat Asn 200	yab	627
0				rgg Trp 205													675
	att Ile	ggt Gly	gag Glu 220	gtg Val	aaa Lys	gat Asp	ggc	ace Tar 225	gta Val	tgt Cys	ggt Gly	oca Pro	gaa Glu 230	aag Lys	atc Ile	tgc Cys	723
s				aag Lys													773
40				tgc Cys													819
s				Cat His													867
0	gga Gly	ggt Gly	agt Ser	gct Ala 285	gat Asp	agt Ser	ggc Gly	cca Pro	cct Pro 290	çet Pro	aag Lys	aac Asn	aac Asn	atg Met 295	gaa Glu	Gly gga	915
ia	tta Leu	aat Asn	gtg Val 300	atg Met	gga Gly	aag Lys	ttg Leu	cgt Arg 365	gga Gly	rct Ser	tgt Cys	gac Asp	aaa Lys 316	act Thr	cac Ris	aca Thr	963
	tgc	cca 1	ccg	tgc	cca	gca	cct	gaa	gc¢	gag	ggc	909	ccg	tea	gte	ttc	
106	Cys		Pro	Cys	Pro	Ala	Pro 320	Glu	Ala	Glu	Gly	Ala 325	Pro	ser	Val	Phe	

	ctc ttc	ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	atc	tcc	cgg	acc	cct
	Leu Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	He	Ser	Arq	Thr	Pro
5	330				335					340					345
	gag gro	aca	tgc	gtg	gtg	gtg	gac	gtg	agc	cac	gaa	gac	cet	gag	gtc
	Glu Val	Thr	Cys		Val	Val	qaA	Val		His	Glu	Asp	Pro		Val
10				350					355					369	
	aag tro	aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	cat	aat	gcc	aag	aça
	Lys Phe	Asn	Trp 365	Tyr	Val	Asp	G3 y	Val 375	Glu	Val	His	Asn	Ala 375	Lys	Thr
15	aag ceg 1203	cgg	gag	gag	cag	tac	aac	agc	acg	tac	egg	gtg	gtc	ago	gue
	Lys Pro	Arg 380	Glu	Glu	Gin	Tyr	Asn 385	Ser	Thr	Tyr	Arg	Val	val	Ser	Val
20	ctc acc	gtc	atg	cac	cag	gac	tgg	ctg	aat	ggc	aag	gag	tac	aag	tgc
	1251 Leu Thr 395	٧al	Leu	His	Gln	Asp 400	Trp	Leu	Asn	Gly	Був 405	Glu	Tyr	Lys	Cys
26	aag gto 1299	tec	aac	aaa	gce	ctc	cca	gce	cce	atc	gag	aaa	acc	atc	too
	Lys Val	Ser	Asn	Lys	Ala 415	Leu	Pro	Ala	Pro	11e 420	Glu	Lys	Thr	lle	Ser 425
\$10	aaa goo 1347	aaa	999	cag	ccc	cga	gaa	cca	çag	gtg	tac	acc	atg	ccc	cca
	Lys Ala	Lys	Gly	Gln 430	Pro	Arg	Glu	Pro	Gln 435	Val	Tyr	Thr	Leu	Pro 440	Pro
35	tcc cgg 1395														
	Ser Arg	Asp	Glu 445	Leu	Thr	Lys	Asn	Gln 450	Val	Ser	Leu	Thr	Cys 455	Leu	Val
	aaa ggc 1443	ttc	tat	ccc	agc	gac	atc	gee	gtg	gag	tgg	gag	agc	aat	999
40	Lys Gly	Phe	Tyr	Pro	Ser	Asp	Ile 455	Ala	Va1	Glu	Trp	Glu 470	Ser	Asn	Gly
	cag ccg	gag	aac	aac	tac	aag	acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac
45	Gln Pro 475	Glu	Asn	Asn	Tyr	Lys 480	Thr	Thr	Pro	Pro	Val 485	Leu	qaA	Ser	Asp
	gge tce 1539														
50	Gly Ser 490	Phe	Phe	Leu	Tyr 495	Ser	Гув	Leu	Thr	Val 500	Asp	Lys	Ser	Arg	Trp 505
	cag cag 1587														
55	Gln Gln	Gly	Asn	Val 510	Phe	Ser	Сув	Ser	Val 515	Met	His	Glu	Ala	Leu 520	Hís

	asc 1632		tac	acg	cag	aag	agc	ctc	tac	crg	tat	ccg	ggt	888	tga	
			Tyr	Thr 525	G3.n.	lys	Ser	Ъец	Sex 530	Leu	Ser	Pro	Gly	Lys 535		
5	acta 1653		ogg (	ceget	tacas	ga t										
10	<210 <211 <212	> 5 > Pi	RT													
	4233	> A1	CERK	icia.	Sec	įueni	ce									
18	<220 <223	> De	sscri olype			E Ar	tifi.	cial	Seq	uenc	e: £	asio	n			
	4400								_	~						
20	Met 1				5					16				-	15	
	Gly	Ser	Thr	Gly 20	Thr	Ser	Сув	Gly	Asn 25	Leu	Val	Val	Glu	Glu 30	Gly	Glu
	Glu	Cys	Asp 35	Сув	Gly	Thr	Ile	Arg	Gln	Cys	Ala	Гуs	Asp	Pro	Cys	Cys
25	Leu	Leu So		Сув	Thr	Leu	His 55		Gly	Ala	Ala	Сув		Phe	gly	lle
	Cya 65		Lys	Aap	Cys	Lys		Leu	Pro	Ser	01y 75		Leu	Cys	Arg	
	Gln	Va.l	gly	Glu			Leu	Pro	Glu			Asn	Gly	Thr		80 Kis
30	Gln	сув	Pro		85 Asp	Val	Tyr	Val		oe qaA	Gly	He	ser		95 Asn	Val
	asa	Ala		Cys	Tyr	Glu	Lys		Cys	Asn	Asn	His	Asp	110	Gln	Cys
	Lys	Glu	3.15 Tle	9hs	Gly	Gln	Asp	120 Ala	Arg	Ser	Ala	Ser	125 Gln	Ser	Cys	Tyr
36	Gln	130 Glu	Ile	naA	Thr		135 Gly	Asn	Arg	Phe	Gly	140 His	Cys	Gly	Tle	Val
	145 Gly	Thr	Thr	Tyr	Val	150 Lys	Cys	Trp	Thr	Pro	155 Asp	Ile	Met	Cys	Gly	160 Arg
	Val	Gln	Cys	Glu	165 Aan	Va1	Gly	Val		1.70 Pro	Asn	Leu	Tle		175 His	Ser
40	Thr	Va1		180 Gln	Phe	His	Leu		185 Asp	Thr	Thr	Cys	Trp	190 Gly	Thr	Asp
	Tyr	His	195 Leu	Gly	Met	Ala	Ile	200 Pro	Asp	Ile	Gly	Glu	205 Val	Lys	Asp	Gly
	Thr	210 Val	Cys	Gly	Pro	Glu	Lys	Ile	Cys	Ile	Arg	220 Lys	Lys	Cys	Ala	ser
45	225 Met					236					235					248
	Gly				245					250					255	-
				260					265					270		
50	Pro		275					280					285			
		290					295					300				
	Arg 305	Gly	Ser	Cys	Asp	110 310	Thr	His	Thr	Cys	Pro 315	Pro	Cys	Pro	Ala	Pro 320
55	Glu .	Ala	Glu	Gly	Ala 325		Ser	Val	Phe	Leu 330		Pro	Pro	Lys	Pro 335	

	A																
	жыр	Thr	Leu		Ile	Ser	Arg	Thr		Glu	Val	Thr	Cys	Val	Val	Val	
	à en	Val.	Car	340	230	200	Thun	c2	345	2 114	Tribe as	X	muse	350 Tyr	20.2	3 mm	
5	Nap	4104.2	355	1112	GIG	wafe	810	360	val	The	Pile	Matt	365	1 yr.	val	ирр	
-	Gly	Val	Glu	Val.	His	Asn		Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gla	Tyr	
		370		-			375					380					
	385	ser	Thr	Tyx	Arg	390	Val	Sec	Val	Leu		Val	Leu	His	Gln		
		Lan	Xen	05.0	Lare		****	2	A	Teve	395		2	Lys	***	400	
10	***		riwac	ory	4.05	GIN	ryr	my s	cys	410	vax	CHE L	ASII	Liya	415	740 ft	
	Pro	Ala	Pro	The		Lys	Thr	Ile	Ser 425		Ala	Lys	Gly	Gln 430		Arg	
	Glu	Pro			Tyr	Thr	Leu			Ser	Arg	Asp		Leu	Thr	Lys	
	Arm	127 m	435	Con	*	Arrilla an	~	440	15- 3			m)	445	W			
18	MOTE	450	V (3 ).	Ser	viesci	THE	455	nea	vatz	nys	ary	450	1yr	Pro	SHOT	Asp	
	rie		Val	din	Tro	Gin		Acn	130	con.	Dro		han	Asn	Trees	Tree	
	465			0.0.0		470		******	UL J		475	u.u	A.O.L.	CAGA	.yr.	480	
	Thr	Thr	Pro	Pro	Val		Asp	Ser	Asp	Gly		Phe	Phe	Leu	Tyr		
					485				٠	490					495		
\$0	Lys	Leu	Thr		Asp	Lys	Ser	Arg		Gln	Gln	Gly	Asn	Val	Phe	Ser	
				500					505					510			
	cyg	ser	515	wer	Hls	GTff	Ala	520	His	Asn	His	Tyr		Gln	Lys	Ser	
	7-011	Day		Ser	Dra	M3	****	520					525				
	June	530	More	261	110	OTA	535										
25																	
	<210	3× 3.	3														
	<22.	1> 21	517														
		2 > 10 2 × 10															
30	<212	2 × 101	A.	icial	l Sec	nen	ce.										
30	<213 <213	2 × 101 3 × A:	A.	icia	l Sec	inev	e e										
30	<213 <213 <220	2 × 101 4 × A: 3 ×	NA rtif														
30	<213 <213 <220	2 × Di 4 × A: 3 × 4 × D:	NA rtif	icia: iptic aptic	on of			cial	seq	sence	e: £1	sion	n				
	<210 <210 <220 <220	2 > Di 1 > A: 2 > 1 > D: p:	NA rtif	iptic	on of			cial	Seq	ienc«	e: fs	sio	n				
30 35	<213 <213 <220 <223	2 > D1 1 > A: 2 > D1 2 > D2 2 > D2	NA rtif sscr	iptic	on of			cial	Seq	ienco	e: fs	sio	2				
	<21: <21: <22: <22: <22: <22:	2 > 101 2 > 4: 3 > 10: 4 > 10: 5 > 10: 6 > 10: 6 > 10: 7 > 10: 8 > 10: 10 >	NA rtif sscr plype	iptic aptic	on oi ie			cial	ಕಕರು	senco	e: Ít	sio	n				
	<21: <21: <22: <22: <22: <22:	2 > 101 2 > 4: 3 > 10: 4 > 10: 5 > 10: 6 > 10: 6 > 10: 7 > 10: 8 > 10: 10 >	NA rtif sscr plype	iptic	on oi ie			cial	Sequ	ience	2: £8	sio	2				
	<210 <211 <220 <220 <220 <220 <220 <200 <400	2 > Di 1 > A: 3 > 4 > D: 5 > 6 > D: 5 > Ci 5	NA rtif sscr: plype 08 25).	iptic aptic	on of ie	£ Axt	ifi										
	<210 <211 <220 <220 <220 <220 <220 <200 <400	2 > Di 1 > A: 3 > 4 > D: 5 > 6 > D: 5 > Ci 5	NA rtif sscr: plype 08 25).	iptic aptic	on of ie	£ Axt	ifi	atg (	jag i	aca g	jac i	ica c	otc (	ctg o	ota t	. <del>2</del> 3	51
95	<210 <211 <220 <220 <220 <220 <220 <200 <400	2 > Di 1 > A: 3 > 4 > D: 5 > 6 > D: 5 > Ci 5	NA rtif sscr: plype 08 25).	iptic aptic	on of ie	£ Axt	ifi	atg (	jag i	aca g	jac i	aca c	otc (	ctg (	ora t	sāā	51
95	<210 <211 <220 <220 <220 <220 <220 <200 <400	2 > Di 1 > A: 3 > 4 > D: 5 > 6 > D: 5 > Ci 5	NA rtif sscr: plype 08 25).	iptic aptic	on of ie	£ Axt	ifi	atg (	jag i	aca g	jac i	ica c	otc (	ctg ( Leu 1	ora t Leu 7	gg Trp	51
95	<221 <221 <222 <222 <221 <223 <400 ghot	2 × Di 2 × A: 3 × Di 4 × Di 5 × Ci 1 × Ci 1 × Ci 1 × Ci 1 × Ci	na rtif: sscr: plype 08 25).	iptic aptic . (15:	on of de de)	E Ari	cifi acc	atg ( Wet (	jag : Slu :	ica (	jac i	aca c thr I	oto o Leu I	Leu I	Leu 7	rp	
95	<211 <211 <222 <223 <222 <221 <220 <400 gtog	2 × Di 1 × A: 2 × Di 2 × Ci 2 × Ci 2 × Ci 3 × Ci 3 × Ci 4 × Ci 5 × Ci 5 × Ci 7	nA rtif sscr plype ss ss).	iptic aptic . (15)	on of de de) getac	ge es	cific	atg ( Wet (	jag i	aca g	ggt	aca chr I	etc ( Leu !	Leu 1	999 999	rp	51
95	<211 <211 <222 <223 <222 <221 <220 <400 gtog	2 × Di 1 × A: 2 × Di 2 × Ci 2 × Ci 2 × Ci 3 × Ci 3 × Ci 4 × Ci 5 × Ci 5 × Ci 7	nA rtif sscr plype ss ss).	iptic aptic . (15)	on of de de) getac	ge es	cific	atg ( Wet (	jag i	aca g	ggt	aca chr I	etc ( Leu !	Leu I	999 999	rp	
38 40	<212 <211 <222 <222 <222 <400 gtog	2 × Di 1 × A: 2 × Di 2 × Ci 2 × Ci 2 × Ci 3 × Ci 3 × Ci 4 × Ci 5 × Ci 5 × Ci 7	nA rtif sscr plype ss ss).	iptic aptic . (15)	on of de de) getac	ge ca	cific	atg ( Wet (	jag i	aca g	ggt Sly	aca chr I	etc ( Leu !	Leu 1	999 999	eat Asn	
38 40	<211	stg	NA rtif: sscr. plypo os ss). scan; ten	ipticaptic	on of the state of	gtr val	cific ecc Pro	atg ( Wet ( 1 ggt Gly	gag : Slu : tcc Ser	aca (Thr act	ggt Gly 20	aca chr I	etc c Leu I agt ser	tgt Cys	999 Gly cag	aat Asn 25	99
38 40	<211	stg	NA rtif: sscr. plypo os ss). scan; ten	ipticaptic	tgg Trp	gtr val	cific ecc Pro	atg ( Wet ( 1 ggt Gly	gag : Slu : tcc Ser	act Thr gac Asp	ggt Gly 20	aca chr I	etc c Leu I agt ser	tgt Cys	999 Gly cag	aat Asn 25	99
38 40	<211	stg	NA rtif: sscr. plypo os ss). scan; ten	ipticaptic	on of the state of	gtr val	cific ecc Pro	atg ( Wet ( 1 ggt Gly	gag : Slu : tcc Ser	aca (Thr act	ggt Gly 20	aca chr I	etc c Leu I agt ser	tgt Cys	999 Gly cag	aat Asn 25	
98 40 45	<211 <212 <222 <222 <222 <400 gtog gtal val 10 ggt Gly	etg theu	NA rtif sscr blyp os 25). ctg Leu gtt Val	iptic eptic .(159 ctc Leu gas Glu	on of the tgg trp aga Arg 30	gtt gtt Val 15 gaa Glu	cifi cca pro gag	atg ( let ( 1 ggt Gly cag	tee ser tgr Cys	act Thr	ggt Gly 20 tgt Cys	aca chr I 5 act Thr 99a 91y	agt agt ser	tgt Cys gta Val	999 Gly cag Gln 40	eat Asn 25 cag Gln	59 14
38 40	<21: <21: <22: <22: <22: <22: <40: gto; gto; Gly	22× Di 22× Di 23× Ai 23× Di 23× Di	NA rtif sscr blyp 08 08 25). ctg Leu gtt Val	iptic eptic .(15: ctc Leu gas Glu	on of de e6) tggctac tgg Trp aga Arg 30	gtr. yal 15 gaa Glu	cific	atg (	gag : toc ser tgr Cys	aca (thr act Thr gac Asp 35	ggt Gly 20 tgt Cys	aca carrier I for	etc (	tgt Cys gta val	999 Gly cag Gln 40	eat Asn 25 Cag Gln	59 14
98 40 45	<21: <21: <22: <22: <22: <22: <40: gto; gto; Gly	22× Di 22× Di 23× Ai 23× Di 23× Di 24× Di 24× Di 25× Di	NA rtif sscr blyp 08 08 25). ctg Leu gtt Val	iptic aptic ctc Leu gaa Glu gac Asp	on of de e6) tggctac tgg Trp aga Arg 30	gtr. yal 15 gaa Glu	cific	atg (	toc Ser tgr Cys	aca (thr act Thr gac Asp 35	ggt Gly 20 tgt Cys	aca carrier I for	etc (	tgt Cys gta val agg Arg	999 Gly cag Gln 40	aat Asn 25 Cag Gln	59 14
98 40 45	<21: <21: <22: <22: <22: <22: <40: gto; gto; Gly	22× Di 22× Di 23× Ai 23× Di 23× Di 24× Di 24× Di 25× Di	NA rtif sscr blyp 08 08 25). ctg Leu gtt Val	iptic eptic .(15: ctc Leu gas Glu	on of de e6) tggctac tgg Trp aga Arg 30	gtr. yal 15 gaa Glu	cific	atg (	gag : toc ser tgr Cys	aca (thr act Thr gac Asp 35	ggt Gly 20 tgt Cys	aca carrier I for	etc (	tgt Cys gta val	999 Gly cag Gln 40	aat Asn 25 Cag Gln	99
98 40 45	<211 <221 <222 <222 <222 <400 gtog  gta 10  ggt  Gly  tgt  tgt	stg val	NA rtif sscr os ss). csa ( teu gtt Val	ctc Leu gaa Glu gac Asp 45	on of de de de de de de de de de de de de de	gtr gtr Val 15 gaa Glu tgt	cific ecca Pro gag Glu tgt Cys	atg (det (det (det (det (det (det (det (det	toc ser tgr Cys	act fir act Thr gac Asp 35	ggt Gly 20 tgt Cys	aca control of the I	agt agt ser tcc ser	tgt Cys gta val agg Arg	ggg Gly cag Gln 40 cct Pro	eat Asn 25 Cag Gln 999	34
98 40 45	<211 <221 <222 <222 <222 <222 <240 <400 <400 <400	stg ctg ctg ctg ctg ctg ctg ctg ctg ctg c	NA rtif sscr plyp SS SS). ctg ttg Caa Gin tgt	ctc Leu gas Glu gsc 45	on on on one of the original	gtr. val 15 gaa Glu tgt. Cys	eca eca Pro gag Glu tgt Cys	atg ( let (	tec ser tgr Cys trg Leu 50	aca gac act Thr act Asp 35	ggt Gly 20 tgt Cys	aca cat Thr I sact Thr Gga act Thr Thr	agt ser too ser cta	tgt Cys gta val agg Arg	ggg Gly cag Gln 40 cct Pro	east Asn 25 cag Gln 999 Gly	99

5													gac				291
	tgg Trp 90	tgc Cys	aat Asn	gga	aca	tet Ser 95	cat	cag Gln	tgt Cys	cca Pro	gaa Glu 100	gat Asp	aga Arg	tat Tyr	gtg Val	cag Gln 105	339
10	gae Asp	617 613	atc	Pro	tgt Cys 110	agt Ser	gac Asp	agt Ser	gce Ala	tac Tyr 115	tge Cys	tat	caa Gln	aag Lys	agg Arg 120	tgt Cys	387
15	naA	Asn	His	125	Gln	Ris	Cys	Arg	Glu 130	Ile	Phe	Gly	aaa Lys	Asp 135	Ala	Lys	435
20	agt Ser	yca Ala	ter Ser 140	cag Gln	aat Asn	tge Cys	rat Tyr	aaa Lys 145	gaa Glu	atc	aac Asn	tet Ser	cag Gln 150	gga Gly	Asn	cgt Arg	483
	Fhe	ggr Gly 155	cac His	tgt Cys	gly	ile	aat Asn 160	ggc ggc	aca Thr	Thr	tac	cta Leu 165	aaa Lys	tgt Cys	cat His	atc 11e	531
25	tet Ser 170	gat Asp	gtc Val	trt Phe	tgt Cys	999 Gly 175	aga Arg	gtt Val	CAA Gln	tgt Cys	gag Glu 180	aat Asn	gtg Val	aga Arg	gac Asp	att Tle 185	579
30	Pro	ett Leu	Ctc	caa Gln	gat Asp 190	cat His	ttt Phe	act Thr	t tg Leu	cag Gln 195	Ris	act Thr	cat His	atc Ile	aat Asn 200	ggt	627
	gts Val	ace Thr	tgc Cys	tgg Trp 205	ggt Gly	att	gac Asp	tat	cat His 210	tta Leu	agg	atg Met	aac Asn	ata Ile 215	tet Ser	gac Asp	675
36	att Ile	ggt Gly	gaa Glu 226	gtg Val	aaa Lys	gat	ggt Gly	act Thr 225	gtg Val	tgt Cys	gly	Pro	gga Gly 230	aag Lys	atc Ile	tgc Cys	723
46	atc Ile	His 235	aag Lys	aag Lys	tgt Cys	gtc Val	agt Ser 240	ctg	tct Ser	gtc Val	ttg Leu	tca Ser 245	cat His	gtc Val	tgc Cys	ctt Leu	771
46	pro 250	gag Glu	Thr	tgc Cys	aat Asn	atg Met 255	aag Lys	G1Å 888	atc Ile	tgc Cys	aat Asn 260	aac Asn	aaa Lys	cat Wis	cac His	tgc Cys 265	819
	cac His	tgt Cys	ggc Gly	tat Tyr	999 Gly 270	tgg Trp	tec	Pro	ecc Pro	tac Tyr 275	tgc Cys	cag Gln	cac Hís	aga Arg	ggc Gly 280	tat Tyr	867
50	g1A aaa													Ser			915
95	aaa Lys	act Thr	cac His	aca	tge Cys	cca Pro	ccg Pro	tgc Cys	cca	gca Ala	cet Pro	gaa Glu	gcc Ala	gag Glu	gg¢ Glv	geg Ala	963
	-		300					305					310	324	227		

	ceg tea	gtc	ttc	ctc	ttc	cce	cca	aaa	ccc	aag	gac	acc	ctc	atg	atc
5	Pro Ser 315	Va3	Phe	Leu	Phe	Pro 320	Pro	Lys	bro	Lys	Asp 325	Thr	Leu	Met	Ile
	tcc cgg	acc	cet	gag	gtc	aca	tge	gtg	gtg	gtg	gac	gtg	age	cac	gaa
10	Ser Arg	The	Pro	Glu	Val 335	Thr	Cys	Vai	Val	Val 340	Asp	Val	Ser	His	G1u 345
	gac cct	gag	gtc	aag	tte	aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	cat
	Asp Pro	Glu	Val	Lys 350	Phe	Asn	Trp	Tyr	Val 355	Asp	Gly	Val	Glu	Va.l. 360	His
15	aat gcc 1155	eag	aca	aag	ccg	cgg	gag	gag	cag	tac	аас	age	acg	tac	cgg
	Asn Ala	Lys	Thr 365	Lys	Pro	Arg	Glu	Gln 370	Gln	Tyr	Asn	Ser	Thr 375	Tyr	Arg
80	gtg gtc	agc	gte	ctc	acc	gte	ctg	cac	cag	gac	tgg	ctg	aat	gge	aag
	Val Val	Ser 380	Val	Leu	The	Val	Leu 385	His	Gln	Asp	Try	Leu 390	Asn	Gly	Lys
.25	gag tac	aag	tgc	aag	gtc	tee	asc	aaa	gcc	cte	cca	gec	ccc	ato	gag
	Glu Tyr 395	Lys	Cys	Lys	Val	Ser 400	Asn	Lys	Ala	Leu	Pro 405	Ala	Pro	Ile	Glu
30	aaa acc 1299	atc	tee	286	gcc	ans	999	cag	occ	ega	gaa	cca	cag	gtg	tac
	Lys Thr 410	Ile	Ser	Lys	31a 415	Lys	Gly	Gln	Pro	Arg 420	Glu	Pro	Gln	Val	Tyr 425
36	acc ctg 1347														
	Thr Leu	Pro	Pro	Ser 430	Arg	Asp	Glu	Leu	Thr 435	Lys	Asn	Gin	Val	Ser 440	Leu
40	acc tgc 1395														
	The Cys	Leu	Val 445	Lys	Gly	Phe	Tyr	Pro 450	Ser	Asp	lle	Ala	Val 455	Glu	Trp
	gag agc 1443														
45	Glu Ser	Asn 460	Gly	Gln	Pro	Glu	Asn 455	Asu	Tyr	Lys	Thr	Thr 470	Pro	Pro	Val
	ctg gac 1491														
30	Leu Asp 475	Ser	Asp	Gly	Ser	Phe 480	Phe	Leu	Tyr	Ser	Lys 465	Leu	Thr	Val	qeA
	aag agc 1539													-	
55	Lys Ser	Arg	Trp	Gln	Gln 495	Gly	Asn	Va1	Phe	Ser 500	Cys	ser	Va1	Met	His 505

gag get eng cac aac cac tac acg cag ang age etc tee eng tet eng 3587 Glu Ala Leu His Asn His Tyr Thr Sln bys Ser Leu Ser Leu Ser Pro ggt aaa tga actagagcgg cogetacaga t 1617 Gly bys <210> 14 <211> 523 <212 > PRT <213> Artificial Sequence ×230× <223> Description of Artificial Sequence: fusion polypeptide <400> 14 Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro 10 Gly Ser Thr Gly Thr Ser Cys Gly Asn Gly Val Val Glu Arg Glu Glu 20 25 Gln Cys Asp Cys Gly Ser Val Gin Glu Cys Glu Gln Asp Ala Cys Cys 35 40 Leu Leu Asn Cys Thr Leu Arg Pro Gly Ala Ala Cys Ala Phe Gly Leu 50 55 Cys Cys Lys Asp Cys Lys Phe Met Pro Ser Gly Glu Leu Cys Arg Glu 70 Glu Val Asn Glu Cys Asp Leu Pro Glu Trp Cys Asn Gly Thr Ser His 85 30 Gin Cys Pro Glu Asp Arg Tyr Val Gin Asp Gly Ile Pro Cys Ser Asp 300 105 110 Ser Ala Tyr Cys Tyr Gln Lys Arg Cys Asn Asn His Asp Gln His Cys 115 125 320 Arg Glu Ile Phe Gly Lys Asp Ala Lys Ser Ala Ser Gln Asn Cys Tyr 135 140 Lys Clu Ile Asn Ser Gln Gly Asn Arg Phe Gly His Cys Gly Ile Asn 150 155 Gly Thr Thr Tyr Leu Lys Cys His Ile Ser Asp Val Phe Cys Gly Arg 165 170 Val Gln Cys Glu Asn Val Arg Asp Ile Pro Leu Leu Gln Asp His Phe 180 185 3.90 Thr Leu Gln His Thr His Ile Asn Gly Val Thr Cys Trp Gly Ile Asp 195 200 205 Tyr His Leu Arg Met Asn Ile Ser Asp Ile Gly Glu Val Lys Asp Gly 210 215 220 Thr Val Cys Gly Pro Gly Lys Ile Cys Ile His Lys Lys Cys Val Ser 230 235 Leu Ser Val Leu Ser His Val Cys Leu Pro Glu Thr Cys Asu Met Lys 250 Gly Ile Cys Asn Asn Lys His His Cys His Cys Gly Tyr Gly Trp Ser 260 265 270 Pro Pro Tyr Cys Gln His Arg Gly Tyr Gly Gly Ser Ile Asp Ser Gly 275 280 Pro Ala Ser Ale Lys Arg Ser Cys Asp Lys Thr His Thr Cys Pro Pro 295 3.00 Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro 310 315

90

25

30

.25

40

45

nn.

	Pro	Lys	Pro	Буз	Asp 325	Thr	Leu	Met	Tle	Ser 330	Arg	Thr	Pro	Glu	Val 335	Thr	
	Çys	Va1	Val	Val 340	Asp	Va I	Ser	Hís			Pro	Glu	Val			Asn	
	Trp	Tyr	Val	Asp		Val	Glu	Val	345 His	Asn	Ala	Lys		350 Lys	Pro	Arg	
	Slu	Glu	355 Gln	Tyr	Asn	Ser	Thr	360 Tyr		Val	Val		365 Val	Len	Thr	Val	
	Lon	370		A	ET-144		375	er		47		380					
2	385	13 4.00	Gitte	Asp	115	390	Ran	GIY	nys	GIA	395	nya	CAR	Lys	Va.l.	Ser 400	
	raA	Lys	Ala	Leu	Pro 405	Ala	Pro	lle	Glu	Lys 410	Thr	Tle	Ser	Lys	Ala	Lys	
	Gly	Gla	Pro	Arg 420	Glu	Pro	Gln	Val	Tyr 425	Thr	Leu	Pro	Pro	Ser 430	Arg	Asp	
5	Glu	Leu	Thr #35	ьув	Asn	Gln	Val	Ser.		Thr	Cys	Leu	Val.	Lys	Gly	Phe	
	Tyr	Pro	Ser	Asp	I1e	Ala	Val		Trp	Glu	Ser	Asn 460		Gln	Pro	Glu	
	Asn			Lys	Thr	Thr		Pro	Val	Leu	Asp		Asp	Glv	Ser	Phe	
	465					470					475					480	
9				Ser	485					490	Ser				495	Gly	
	Asn	Val	Phe	Ser	Cys	ser	Val	Met		Glu	a.l.a	Leu	His		His	Tyr	
	Thr	Gln	Lyr	500 Ser	Less	Ser	Len	Ser	505 Pro	Gly	Tare			510			
5			515					520			-Jy 6						
	-210																
	<210																
	<233																
			NT.														
,		> Di > A:		icia:	L Spr	men	re.										
0	<213	5> A:		icia	i Sec	piene	je										
	<213 <220	5> A:	rtif														
	<213 <220	i> Ai	rtif	icia) iptic eptic	n oi			cial	Sequ	ience	ı Li	sion	1				
	<213 <220	i> Ai i> De po	rtif	iptic	n oi			cial	Sequ	ience	ı fı	sion	1				
	<220 <223 <223 <220 <221	i> Ai i> De pc i> CT	sser olyp	iptic eptic	on of			cial	Sequ	ience	ı: fı	rsion	1				
	<220 <223 <223 <223 <223	i> Ai i> De p i> Ci i> (2	escr olypos os os	iptic	on of			cial	Sequ	sence	ı fı	rsion	1				
ş	<220 <223 <223 <220 <221 <222 <400	A	escr olypos os os os	iptic eptic	on of ite	. Art	:ifi										
\$	<220 <223 <223 <220 <221 <222 <400	A	escr olypos os os os	iptic eptic	on of ite	. Art	ific		jag a	ıca g	jac s	ıca c	ete e	tg c	eta t	aa aa	5
ş	<223 <226 <223 <221 <222 <400 gtog	i> A: i> De i> De i> Cr	rtif	iptid eptid - (165 getgg	on of le	f Art	ific	atg q det (	gag a Nu 1	ica ç hr A	ac s	ca c hr I 5	ete c	eu I	eu T	rp aat	5.
ş	<223 <226 <223 <221 <222 <400 gtog	i> A: i> De i> De i> Cr	rtif	iptid eptid - (165	on of le	f Art	ific	atg q det (	gag a Nu 1	ica ç hr A	ac s	ca c hr I 5	ete c	eu I	eu T	rp aat	
ş	<220 <223 <223 <221 <222 <400 gteg gta Val 10	is like like like like like like like like	rtif escr olyp os ss). s caa  ctg teu	iptic eptid - (165  ctg:  ctc  teu	on of le	ge ca get Val 15	cca pro	atg g det d l ggr Gly	jag a Slu 1 tee Ser	aca g hr A act Thr	gac s sp T ggt Gly 20 ten	ca c hr I 5 act Thr	ete e æu L agt ser	eu 1 tgt Cys	ggc Gly	aat Asn 25	9
,	<220 <223 <223 <221 <222 <400 gteg gta Val 10	is like like like like like like like like	rtif escr olyp os ss). s caa  ctg teu	iptid eptid - (165 getgg	teg Trp	ge ca get Val 15	cca pro	atg g det d l ggr Gly	jag a Slu 1 tee Ser	ica g Thr A act Thr gat Asp	gac s sp T ggt Gly 20 ten	ca c hr I 5 act Thr	ete e æu L agt ser	eu 1 tgt Cys	ggc Gly	aat Asn 25	
ş	<220 <223 <223 <221 <222 <400 gteg gta Val 10	is like like like like like like like like	rtif escr olyp os ss). s caa  ctg teu	iptic eptid - (165  ctg:  ctc  teu	on of le	ge ca get Val 15	cca pro	atg g det d l ggr Gly	jag a Slu 1 tee Ser	aca g hr A act Thr	gac s sp T ggt Gly 20 ten	ca c hr I 5 act Thr	ete e æu L agt ser	eu 1 tgt Cys	ggc Gly	aat Asn 25	9
ş	<220 <223 <220 <223 <222 <400 gtog gta Val 10 ggc Gly	is A: is De po is De po is Ci	rtif esser olypo os os os cs ctg leu alt lle	iptic eptid - (165 ctc Lea gaa Gio	tgg Trp	get ca get Val 15	ecc :	atg det det de det de	gag a Slu 1 tee ser tgt Cys	act Thr	ac s sp T ggt 20 20 tgt	ca c hr I s act Thr gga Gly	agt ser acc	eu 1 tgt Cys ccg Pro	ggc Gly gcc Ala	rp aat Asn 25 gaa Glu	9
,	<220 <220 <221 <221 <222 <400 gtog gta Vai 10 ggc Gly	is A: is Dis is Dis px is Ci;	rtiff sscr olyp os os os ctg teu alt ile	iptic eptid - (165  ctg:  ctc  teu	tgg Trp act 30	get cage cage	cea pro gag gaq	atg colet ( ) ggr Gly gag Glu	gag a klu 1 tee Ser tgt Cys	act Thr A	ggr sggr ggr 20 tgr Cys	ca c hr I s act Thr gga Gly	ete c eu l agt ser acc Thr	eu I tgt Cys ccg Pro	ggc Gly gcc Ala 40	rp aat Asn 25 gaa Glu	9
	<220 <223 <223 <221 <222 <400 gtog gta Val 10 ggc Gly	is A: is IN	rtif escr olyp os sss, caa ctg leu alt lle	ctc Leu gaa Glu as	tegs Trp act 30	get cage cage cage cage cage cage cage cage	gag Glu	atg g let ( ggr Gly gag Glu tgt Cys	tgt Cys tgt Cys	act Thr A act Thr Sat Asp 35	ac s sp T ggt 20 20 tgs Cys asa	ca chr I 5 act Thr Gga Gly tgc	agt ser acc Thr	eu I tgt Cys ccg Pro ttg Leu 55	ggc Gly gcc Ala 40 act	aat Asn 25 gaa Glu caa Gln	9
	<220 <220 <221 <221 <222 <400 gtog gta Vai 10 ggc Gly	is Ai is Inc. is Inc. is Inc. is Inc. is City (2 is City (2 is Inc. is City (2 is Inc. is City (2 is Inc. is I	rtif escrippo OS 25). 5 ctg heu alt lie ctt Leu caa	iptic eptic (165 ctc Leu gaa Glu a5	teg trp act Thr 30 gga sly	get ca get val 15 gga gly gca Ala	cea Pro gag Glu	det (  ggr gag glu tgt Cys	gag a sellu 1 tee Ser tgt Cys tgt Cys 50	hr A act Thr gat Asp 35 aag Lys	ggt ggt 20 tgt Cys	ca con the I same the	agt ser acc Thr	eu I tgt Cys ccg Pro ttg Leu 55	ggc Gly gcc Ala 40 act	aat Asn 25 gaa Glu caa Gln	9

	ect Pro	atg Met 75	ggc Gly	act Thr	gtg Val	tgc Cys	cga Arg 80	gaa Glu	gca Ala	gta Val	aat Asn	gat Asp 85	tgt Cys	gat Asp	att	egt	293
ş	gaa Glu 90	acg Thr	tgc Cys	tca Ser	gga Gly	aat Asn 95	tca Ser	agc	cag Gln	tgt Cys	gcc Ala 100	oct	aat Asp	att	cat Ris	aaa Lys 105	339
10							gat Asp										387
15	aga Arg	tgc Cys	aaa Lys	acc Thr 125	aga Arg	gat Asp	aga Arg	caa Gln	tgc Cys 130	aaa Lys	tac	att	tgg Trp	999 Gly 135	caa Gln	Lys	435
							rat Tyr										483
eo	acg	gag Glu 185	aag Lys	ggt Gly	aac Asn	tgt Cys	160 GJA GGG	aaa Lys	gac Asp	aaa Lys	gac Asp	aca Thr 165	tgg Trp	ata Ile	cag Gln	tgc Cys	531
ts .							tgt Cys										579
10							gaa Glu										627
							aca Thr										675
গ্ৰ	ctr Leu	gaa Glu	gaa Glu 220	gat Asp	gta Val	gat Asp	ctt Leu	ggc Gly 225	tat Tyr	gtg Val	gaa Glu	gat Asp	999 Gly 230	aca Thr	cct	tgt Cys	723
10	ggt Gly	ccc Pro 235	caa Gln	atg Met	atg Met	ege	rta Leu 240	gaa Glu	cac His	agg	tgt Cys	ctt Leu 245	cet	gtg Val	got Ala	tot Ser	771
15	ttc Phe 250	aac Asn	ttt Phe	agt Ser	act Thr	tgc Cys 255	ttg Leu	agc Ser	agt Ser	aaa Lys	gaa Glu 250	ggc Gly	act	att Ile	tge Cys	tca Ser 265	819
	gga Gly	aat Asn	gga Gly	gtt Val	tgc Cys 270	agt Ser	aat Asn	gag Glu	ctg Leu	aag Lys 275	tgt Cys	gtg Val	tgt Cys	aac Asn	aga Arg 280	cac His	867
10	tgg Trp	ata	ggt Gly	tot Ser 285	gat Asp	tge Cys	aac Asn	act Thr	tac Tyr 290	ttc Phe	cct Pro	cac His	aat Asn	gat Asp 295	gat Asp	gca Ala	915
25	aag Lys	act Thr	ggt Gly	atc	act	ctg Leu	bot Ser	ggc Gly	aat Ass	ggt Gly	gtt Val	gct Ala	ggc	acc Thr	aat Asn	gga Glv	963

	tor tgt	gac	aaa	act	cac	aca	tgc	cca	ccg	tgc	çça	gca	cct	gaa	gec
5	Ser Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala
	gag ggc 1059	äcâ	ccg	t.ca	gtc	ttc	ctc	tte	ccc	cca	ass	cce	aag	gac	acc
	Gla Gly	Ala	Pro	Ser		Phe	Læu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr
10	330				335					340					345
	ctc atg	ate	tee	cgg	acc	oct	gag	gtc	aça	tgc	gtg	gtg	gtg	gac	gtg
	Leu Mer	Tle	Ser		Thr	Pro	Glu	Val		Сув	Val	Val	Val		Val
16				350					355					360	
	ago cac	gaa	gac	act	gag	gtc	aag	ctc	aac	tgg	tac	gtg	gac	9gc	gtg
	Ser His	Glu	Asp 365	Pro	Glu	Val	Lys	Phe 370	asn	Trp	Tyr	Val	Asp 375	Gly	Val
20															
60	gag gtg 1203														
	Glu Val	His 380	Asn	Ala	Lys	Thx:	Lys 385	Pro	Arg	Glu	G).u	Gln 390	Tyr	Asa	ser
		300					363					390			
25	acg tac 1251														-
	Thr Tyr	Arg	Val	Val	Ser		Leu	Thr	Val	Leu		Gln	Asp	Trp	Leu
	335					400					405				
367	aat ggc 1299	aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	äaa	acc	ctc	cca	goc
	Asn Gly	PAR	Glu	Tyr	Lys	Су≲	Lys	Val	Ser		Lys	Ala	Leu	Pro	
	410				415					420					425
35	ccc atc	gag	aaa	acc	atc	tee	aaa	gcc	aaa	999	cag	ccc	cga	gaa	cca
CIO .	Pro Ile	Glu	Lys	Thr	He	Ser	Lvs	Als	Lvs	Glv	Gln	Pro	Ara	Glu	Pro
				430			•		435					440	
	cag grg	tac	acc	ctg	ccc	cca	tcc	cgg	gat	gag	ctg	acc	aag	aac	cag
40	Gln Val	Tyr	Thr	Leu	Pro	Pro	ser	Arg	Asp	Glu	Len	Thr	Lys	Asn	Gln
			445					450					455		
	gtc age	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	ccc	age	gac	ato	gec
48	1443 Val Ser	T.011	Whe	Core	3.av	37-23	Tim	<i>(</i> )	The	770	n	·		×1	* 2 -
	7442 202	460	****	Cys	Med	vai	465	Gry	rue	IŽI	110	470	Asp	TIE	ALR
	gtg gag	tgg	gag	agc	aat	999	cag	ccg	gag	aac	aac	tac	aag	acc	acg
	1491 Val Glu	West.	orn	Cav	2 en	nle	23 m	Buon	910	×nm	0.00	No. com	T	mh	vest
50	475	463	314	SEE	chest	480	SH	rro	atn	WEB	485	ryr	nλę	1,1100	THE
	oct ccc 1539	gtg	ctg	gac	tcc	gac	99¢	tcc	ttc	ttc	ctc	tac	age	aag	ctc
	Pro Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu
58	490			-	495		-			500				27	505

```
acc 9tg gas aag ags agg tgg cag cag 9gg aac gtc ttc tca tgc tos
           3587
           Thr Val Asp bys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
3
           gtg atg cat gag get etg cac aac cac tac acg cag aag age etc tee
           Val Met His Glu Ala beu His Asn His Tyr Thr Gln Lys Ser beu Ser
                                           530
           ctg tct ceg ggt aan tga actagagegg cegetacaga t
           Leu Ser Pro Gly Lys
                   540
13
           <210> 16
           <211> 542
           c212> PRT
           <213> Artificial Seguence
20
           <223> Description of Artificial Sequence: fusion
                polypeptide
           <400> 16
           Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Trp Val Pro
                                               10
           Gly Ser Thr Gly Thr Ser Cys Gly Asn Gly Phe Ile Glu Thr Gly Glu
                        20
                                           25
           Glu Cys Asp Cys Gly Thr Pro Ala Glu Cys Val Leu Glu Gly Ala Glu
                                       40
                                                           45
30
           Cys Cys Lys Lys Cys Thx Leu Thx Gln Asp Ser Gln Cys Ser Asp Gly
                50
                                   55
                                                       60
           Leu Cys Cys Lys Lys Cys Lys Phe Gln Pro Met Gly Thr Val Cys Arg
            65
                                70
                                                   75
           Glu Ala Val Asn Asp Cys Asp Ile Arg Glu Thr Cys Ser Gly Asn Ser
25
                            28
                                                90
           Ser Gla Cys Ala Pro Asa Ile His Lys Met Asp Gly Tyr Ser Cys Asp
                       100
                                          105
                                                              110
           Gly Val Gin Gly Ile Cys Phe Gly Gly Arg Cys Lys Thr Arg Asp Arg
                                      120
           Gln Cys Lys Tyr Ile Trp Gly Gln Lys Val Thr Ala Ser Asp Lys Tyr
465
                                  135
                                                      140
           Cys Tyr Glu bys Leu Asn Ile Glu Gly Thr Glu bys Gly Asn Cys Gly
                              150
                                                155
           Lys Asp Lys Asp Thr Trp Ile Gln Cys Asn Lys Arg Asp Val Leu Cys
                          255
                                              170
                                                                  175
           Gly Tyr Leu Leu Cys Thr Asn Ile Gly Asn Ile Pro Arg Leu Gly Glu
45
                                          185
           Leu Asp Gly Glu Ile Thr Ser Thr Leu Val Val Gin Gln Gly Arg Thr
                                      200
                                                          205
           Leu Asn Cys Ser Gly Gly His Val Lys Leu Glu Glu Asp Val Asp Leu
               230
                                  215
                                                      220
50
           Gly Tyr Val Glu Asp Gly Thr Pro Cys Gly Pro Gln Met Met Cys Leu
           225
                               230
                                                   235
           Glu His Arg Cys Leu Pro Val Ala Ser Phe Asn Phe Ser Thr Cys Leu
                          245
                                              250
           Ser Sex bys Glu Gly Thr Ile Cys Ser Gly Asn Gly Val Cys Ser Asn
                       260
                                          265
                                                              270
           Glu Lea Lys Cys Val Cys Asn Arg His Trp Ile Gly Ser Asp Cys Asn
```

			275					280					285			
		290					Asp 295					300				
5	Gly 305	Asn	Cly	7al	Ala	Gly 310	Thr	Asn	Gly	Ser	Cys 315	Asp	Lys	The	His	Thr 320
		Pro	Pro	Cys	Pro 325		Pro	Glu	Ala			Ala	Pro	ser		
	Leu	Phe	Pro			Pro	Lys	Asp		130 Leu	Met	Tle	ser		335 Thr	Pro
10	Glu	Val	Thr	340 Cys	Val	Val	Val	Asp	345 Val	Ser	Ris	Glu	Asp	350 Pro	Glu	Val.
			355				Asp	350					365			
		370					375 Tyr					380			-	
46	385	X.L.O	200.3	G2 G	JIU	390	ryr	700H	261	2012	395	wiñ	Vest	val	ser	400
7.5	Leu	Thr	Val	î.eu	His 405	Gln	Asp	Trp	Leu	Asn 430		rys	Glu	Tyr	Lys 415	
	Lys	Val	Ser	Asn 420		Ala	Leu	Pro	Ala 425		Ile	Glu	Lys	Thr		Ser
80	Lys	Ala	Lys 435		Gln	Pro	Arg	Glu 440		Gln	Val	Tyr	Thr		Pro	Pro
20	Ser	Arg		Glu	Leu	Thr	Lys		Gln	Val	Ser			Cys	Leu	Val
	Lys		Phe	Tyr	Pro	Ser	455 Asp	Tim	ala.	Val	G) 11	460 Tro	aru.	Ser	ben	GT v
	465					470					475					480
25	Gln	Pro	Glu	Asn	Asn 485	Tyr	Lys	Thr	Thr	Pro 490	Pro	Val	Leu	Asp	Ser	Asp
	Gly	Ser	Phe	Phe 500	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser 510		Trp
	Gln	Gln	Gly 515		Val.	Phe	Ser	Cya 520		va1	Met	His	Glu S25		Leu	His
30	Asn	His 530		Thr	Gln	Lys	Ser 535		Ser	Leu	Ser	Pro 540		Lys		
												345				
	<210															
95	<211	> 2.6	883													
35	<211	> 1.6 > Di	883 IA	icia:	L Sec	roen	ce									
35	<211 <212 <213 <223	> 16 > Di > As	68 FA rtiE:													
95 4G	<211 <212 <213 <223	> 1.6 > Di > As > De	68 IA tif:		on of		ce tific	cial	Sequ	ence	z; Ét	usion	1			
	<211 <212 <213 <223	> 16 > Di > As > De po	68 IA tif:	iptio	on of			cial	Sequ	ence	e; ft	sion	1			
	<211 <212 <213 <223 <223	> 16 > Di > As > De po	668 WA stif: ssor: olype	iptio	on of			cial	Sequ	aence	s; ft	sion	1			
	<211 <212 <213 <223 <223	> 16 > Di > As > De > De	668 MA :tif: :scr: olype	iptic eptic	on oi le			cial	Sequ	aence	e; fl	sio	1			
	<211 <212 <213 <223 <223 <223	> 16 > Di > As > De PC > Ci > (2	668 WA rtif: ser: olype SS (5).	iptic eptic	on oi le			cial	Sequ	ence	e; fi	union	1			
40	<211 <212 <213 <223 <223 <223 <223 <223	> 16 > Dh > An > De > Ci > Ci > Ci	see secretife secretife olype os secretife	iptic	on of le	f Art	tific	ıtg ç	jag a	вса с	gac s	aca c	oto e			
40	<211 <212 <213 <223 <223 <223 <223 <223	> 16 > Dh > An > De > Ci > Ci > Ci	see secretife secretife olype os secretife	iptic	on of le	f Art	tific	ıtg ç	jag a	вса с	gac s	aca c	oto e	etg ( Leu I		
40	<211 <212 <213 <223 <223 <220 <221 <222 <400 gtog	> li > Di > Ai > Di > Ai > De po  Ci > Ci	ses A rtif: clype S (5)	iptic eptic (154	on of le 17) getag	f Art	tific	itg gitet (	gag a	sca (Thr )	gac s Asp 1	aca o	ete d Leu l	keu I	gga	erp aat
4G	<211 <212 <213 <223 <223 <220 <221 <220 <231 <220 <251	> li > Di > Ai > Di > Ai > De po  Ci > Ci	ses A rtif: clype S (5)	iptic eptic (154	on of le 17) getag	f Art	tific	itg gitet (	gag a	sca (Thr )	gac s Asp 1	aca o	ete d Leu l	keu I	gga	erp aat
4G	<211 <212 <213 <223 <223 <223 <220 <221 <222 <400 gtog	> 16 > De la	see NA rtif: resor: objype 25). rcas ; ctg Leu	iptio	on of le	f Art greet general greet gree	ace ace ace ace ace	etg get Gly	gag aglu 1	act Thr	gac s Asp 1 ggt Gly 20 tot	aca of fhr I 5 act Thr	agt Ser	tgt Cys	gga Gly	aat Asn 25

	tgc Cys	tat	99a Gly	Leu 45	tgc Cys	tgt Cys	aag Lys	aaa Lys	tgt Cys 50	tec Ser	Ctc	tec	aac Asn	999 Gly 55	9ct Ala	cac His	195
ā	cys	age	gac Asp 60	91y	ece Pro	tge Cys	tgt Cys	aac Asn 65	ast	ace	tca Ser	tgt Cys	ctt Leu 70	ttt Phe	cag Gln	cca Pro	243
10	cga Arg	999 Gly 75	tat Tyr	gaa Glu	tgc Cys	cgg Arg	gat Asp 80	gct Ala	gtg Val	aac Asu	gag Glu	tgt Cys 85	gat Asp	att Ile	act	gaa Glu	291
18														cat Bis			339
	gac Asp	gga Gly	tat	gca Ala	tgc Cys 110	aat. Asn	caa Gln	aat Asn	cag Gln	ggc Gly 115	egc	tgc Cys	tac Tyr	aat Asn	ggc Gly 120	gag Glu	387
20	tgc Cys	Lys	gcc Ala	aga Arg 125	gac	aac Asn	cag Gln	tgt Cys	cag Gln 130	tac	atc Tle	tgg Trp	gga Gly	aca Thr 135	aag Lys	gct Ala	435
28	gea	617 888	tot Ser 140	gac Asp	Lys	ttd Phe	tgc Cys	tat Tyr 145	gaa Glu	aag Lys	ctg Leu	aat Asn	aca Thr 150	gaa Glu	Gly	act Thr	463
302	gag Glu	aag Lys 155	gga Gly	Asn	cys	g1y 999	aag Lys 160	gat Asp	gga Gly	gac Asp	Arg	tgg Trp 165	att	cag Gln	tge Cys	age Ser	531
														Leu			579
95	gct Ala													act			627
44	tac Tyr	cat His	caa Gln	990 61y 205	arg	gtg Val	Ile	gac	tgc Cys 210	agt Ser	ggt. Gly	gcc Ala	cat His	gta Val 215	gtt Val	tta Leu	675
														cca Pro			723
45														caa Gln			771
δū	aat Aøn 250	atg	agc Ser	agc Ser	tgt Cys	cca Pro 255	ctc	gat	toc Ser	aag Lys	ggt Oly 260	asa	gto Val	tgt Cys	tog	99c 61y 265	819
55	cat His	ggg Gly	gtg Val	tgt Cys	agt Ser 270	aat Asn	gaz Glu	gcc Ala	acc Thr	cge Cys 275	att Ile	tgt Cys	gat Asp	ttc Phe	acc Thr 280	tgg Trp	867

		999 Gly															915
5														~~~			
	Pro	aag Lys	gat Asp 300	gaa Glu	gga Gly	Pro	aag Lys	ggt Gly 305	Pro	agt Ser	Ala	acc	aat Asn 310	aga Arg	tct Ser	tgt Cys	963
10	gac 101	aaa 1	act	cac	aca	tgc	cca	ccg	tgc	cca	gça	cct	gas	gcc	gag	ggc	
	Asg	129 315		His	Thr	Cys	270 320	Pro	Cys	Pro	Ala	Pro 325	Glu	Ala	Glu	Gly	
TS.	gcg 105	ecg	tca	gtc	ttc	ctc	tte	ccc	cca	aaa	ccc	aag	gac	acc	cte	atg	
	Ala 330	Pro	Ser	Val	Phe	Leu 335	Phe	Pro	Pro	Lys	Pro 340	Lys	Asp	Thr	Leu	Met 345	
	atc 110	ree 7	egg	acc	oct	gag	gte	aca	tge	gtg	gtg	gtg	gaç	gtg	agc	cac	
50	Ile	Ser	Arg	The	Pro 350	Glu	Val	Thr	Cys	Val 355	ya1	Val	Asp	Val	Ser 360	His	
	115																
25	Glu	Asp	Pro	365	Val	Lys	Phe	naA	Trp 370	Tyr	Val	Asp	Gl.y	Val 375	Glu	Val	
	120																
30	His	. Ast	Ala 380	Lys	Thr	Lys	Pro	Arg 385	Glu	Glu	Gln	īyr	Asn 390	Ser	Thr	Tyr	
	ogg	gtg 1	gtc	age	gtc	ctc	acc	gte	ctg	cac	cag	gac	tgg	ctg	aat	ggc	
36	Arg	395	Val	Ser	Val	Leu	Thr: 400	Val	Leu	Hi.s	Gln	Asp 405	Trp	Leu	Asn	Gly	
	mag 129	gag 9	tac	aag.	tge	aag	gtc	tcc	aac	aaa	gcc	etc	cca	gaç	ccc	atc	
	Lys 410	Glu	Tyr	Lys	Cys	Lys 415	Val	Ser	Asn	Lys	Ala 420	Leu	Pro	Ala	Pro	Tle 425	
40	gag 134	aaa 7	acc	atc	tcc	aaa	gec	aaa	999	cag	ccc	cga	gaa	cca	cag	gtg	
		Lys	Thr	Ile	Ser 430	Lys	Ala	Lys	Gly	Gln 435	Pro	Arg	Glu	Pro	Gln 440	Val	
45	tac 139	acc 5	etg	cce	cca	tac	ogg	gat	gag	ctg	acc	aag	aac	cag	gtç	agc	
	Tyr	Thr	Leu	Pro 445	Pro	Ser	arg	Asp	61u 450	Leu	Thr	Lys	Asn	Gln 455	Val	Ser	
50	144																
	Leu	Thr	Cys 460	Leu	Val	Lys	Gly	Phe 465	Tyr	Pro	Ser	Asp	11e 470	Ala	Val	Glu	
55	149																
	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	asa	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	

		475					480					485				
	g 0g 153		gac	tcc	gac	ggc	tec	tte	tto	acc	tac	agc	aag	ctc	acc	gtg
9			Asp	Ser	agn	GTu	Ser	Phe	Dne	Fami	Waxe.	Car	Tree	7.00	man	Va.
	490				· Aug	495					500	001	Dyn	Den	1194	505
	gac 158	aag 7	agc	agg	tgg	cag	cag	999	aac	gto	tte	trea	tgc	tee	gtg	atg
10	Asp	Lys	Sex	Arg	Trp	Gln	Gln	Gly	Asn	Val 515	Phe	Ser	Cha	Ser	Val 520	
	163	5						tac								
16	His	Glu	Ala	Leu 525	His	Asn	His	Tyr	Thr 530	Gln	Lys	Sex	Leu	Ser 535	Leu	Sec
	00g	ggt. 8	888	tga	act	agag	cgg	cege	taca	ga t						
	Pro	Gly														
20			540													
	<21	0> 1:	8													
		1> 5														
95		2> 23														
	421	3 × A:	rear:	icia.	i Se	guen	ce									
	<22	0>														
	<22	3 × 100	escr:	iptic	on o	E Ar	tifi	cial	Seq	ence	e: fe	sio	Œ			
			olyp:	eptic	je											
30		pq		eptic	ie.											
30	<40	) 12 < 0	8			Leu	Leu	Leu	Trp	Va1	Leu	Leu	Len	מדנ"	Va1	Pro
30	<40 Met 2	po Glu	g Thr	Asp	Thr			Leu		10					15	
	440 Mec 2 Gly	po Glu Ser	Thr Thr	Asp Gly 20	Thr S Thr	Ser	Cys	Gly	Asn 25	Gly	Tyr	Val.	Glu	Ala 30	15 Gly	Glu
30 35	<40 Mec 2 Gly Glu	Ser Cya	Thr Thr Asp 35	Asp Gly 20 Cys	Thr S Thr Gly	Ser Phe	Cys His	Gly Val	Asn 25 Glu	10 Gly Cys	tyr tyr	Val Gly	Glu Leu 45	Ala 30 Cys	15 Gly Cys	Glu Lys
	<40 Met 2 Gly Glu Lys	Ser Cya Cya 50	Thr Thr Asp 35 Ser	Asp Gly 20 Cys Leu	Thr S Thr Gly Ser	Ser Phe Asn	Cys His Gly 55	Gly Val 40 Ala	Asn 25 Glu His	Cys Cys Cys	Tyr Tyr Ser	Val Gly Asp 60	Glu Leu 45 Gly	Ala 30 Cys Pro	15 Gly Cys Cys	Glu Lys Cys
35	<40 Met 2 Gly Glu Lys	Ser Cya Cya 50	Thr Thr Asp 35 Ser	Asp Gly 20 Cys Leu	Thr S Thr Gly Ser	Ser Phe Asn	Cys His Gly 55	Gly Val	Asn 25 Glu His	Cys Cys Cys	Tyr Tyr Ser Gly	Val Gly Asp 60	Glu Leu 45 Gly	Ala 30 Cys Pro	15 Gly Cys Cys	glu Lys Cys Asp
	<40 Met 2 Gly Glu Lys Asn 65 Ala	Ser Cya Cya Cya So Asn Val	Thr Thr Asp 35 Ser Thr	Asp Gly 20 Cys Leu Ser Glu	Thr S Thr Gly Ser Cys Cys 85	Ser Phe Asn Leu 70 Asp	Cys His Gly 55 Phe Tle	Gly Val 40 Ala Gln Thx	Asn 25 Glu His Pro Glu	10 Gly Cys Cys Arg Tyr 96	Tyr Tyr Ser Gly 75 Cys	Val Gly Asp 60 Tyr	Glu Leu 45 Gly Glu Glu	Ala 30 Cys Pro Cys Asp	15 Gly Cys Cys Arg Ser 95	Gly Lys Cys Slu
35	<a0 Met 2 Gly Glu Lys Asn 65 Ala</a0 	po Glu Ser Cya Cya So Asn Val	Thr Thr Asp 35 Ser Thr Asn	Asp Gly 20 Cys Leu Ser Glu Pro 100	Thr S Thr Gly Ser Cys Cys 85 Asn	Ser Phe Asn Leu 70 Asp	Cys His Gly 55 Phe Tle	Gly Val 40 Ala Gln Thx Lys	Asn 25 Glu His Pro Glu Glu Gln 105	10 Gly Cys Cys Arg Tyr 96 Asp	Tyr Tyr Ser Gly 75 Cys	Val Gly Asp 60 Tyr Thr	Glu Leu 45 Gly Glu Gly Ala	Ala 30 Cys Pro Cys Asp Cys 110	15 Gly Cys Cys Arg Ser 95 Asn	Glu Cys Asp 80 Gly Gln
35 40	<a0 Met 2 Gly Glu Lys Asn 65 Ala</a0 	po Glu Ser Cya Cya So Asn Val	Thr Thr Asp 35 Ser Thr Asn	Asp Gly 20 Cys Leu Ser Glu Pro 100	Thr S Thr Gly Ser Cys Cys 85 Asn	Ser Phe Asn Leu 70 Asp	Cys His Gly 55 Phe Tle	Gly Val 40 Ala Gln Thx Lys Gly	Asn 25 Glu His Pro Glu Glu Gln 105	10 Gly Cys Cys Arg Tyr 96 Asp	Tyr Tyr Ser Gly 75 Cys	Val Gly Asp 60 Tyr Thr	Glu Leu 45 Gly Glu Gly Ala Arg	Ala 30 Cys Pro Cys Asp Cys 110	15 Gly Cys Cys Arg Ser 95 Asn	Glu Cys Asp 80 Gly Gln
35	<pre>&lt;400 Met 2 Gly Glu Lys Asn 65 Ala Gln Asn Cys</pre>	po Glu Ser Cys 50 Ass Val Cys Gln Gln 130	Thr Thr Asp 35 Ser Thr Asn Pro Gly 115 Tyr	Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg	Thr S Thr Gly Ser Cys 85 Asn Cys	Ser Phe Asn Leu 70 Asp Leu Tyr	Cys His Gly 55 Phe Ile His Asn Thr	Gly Val 40 Ala Gln Thx Lys Gly 120 Lys	Asn 25 Glu His Pro Glu Glu 105 Glu Ala	Gly Cys Cys Arg Tyr 96 Asp Cys	Tyr Tyr Ser Gly 75 Cys Gly Lys	Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140	Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp	Ala 30 Cys Pro Cys Asp Cys 110 Asp	15 Gly Cys Cys Arg Ser 95 Asn Asn	Glu Lys Cys Asp S0 Gly Gln Gln Cys
35 40	<a0 2="" me<="" met="" th=""><th>po Glu Ser Cys 50 Ass Val Cys Gln Gln 130</th><th>Thr Thr Asp 35 Ser Thr Asn Pro Gly 115 Tyr</th><th>Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg</th><th>Thr S Thr Gly Ser Cys 85 Asn Cys</th><th>Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thx</th><th>Cys His Gly 55 Phe Ile His Asn Thr</th><th>Gly Val 40 Ala Gln Thx Lys Gly 120</th><th>Asn 25 Glu His Pro Glu Glu 105 Glu Ala</th><th>Gly Cys Cys Arg Tyr 96 Asp Cys</th><th>Tyr Tyr Ser Gly 75 Cys Gly Lys Gly</th><th>Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140</th><th>Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp</th><th>Ala 30 Cys Pro Cys Asp Cys 110 Asp</th><th>15 Gly Cys Cys Arg Ser 95 Asn Asn</th><th>Glu Lys Cys Asp 80 Gly Gln Gln Cys Lys</th></a0>	po Glu Ser Cys 50 Ass Val Cys Gln Gln 130	Thr Thr Asp 35 Ser Thr Asn Pro Gly 115 Tyr	Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg	Thr S Thr Gly Ser Cys 85 Asn Cys	Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thx	Cys His Gly 55 Phe Ile His Asn Thr	Gly Val 40 Ala Gln Thx Lys Gly 120	Asn 25 Glu His Pro Glu Glu 105 Glu Ala	Gly Cys Cys Arg Tyr 96 Asp Cys	Tyr Tyr Ser Gly 75 Cys Gly Lys Gly	Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140	Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp	Ala 30 Cys Pro Cys Asp Cys 110 Asp	15 Gly Cys Cys Arg Ser 95 Asn Asn	Glu Lys Cys Asp 80 Gly Gln Gln Cys Lys
35 40 45	<a0 1="" 1<="" met="" td=""><td>po Glu Ser Cys 50 Ass Val Cys Gln Gln Glu</td><td>Thr Thr Asp 35 Ser Thr Asn Pro Gly 115 Tyr Lys</td><td>Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg Ile Leu</td><td>Thr S Thr Gly Ser Cys 85 Asn Cys Trp Asn Trp</td><td>Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thr</td><td>Cys His Gly 55 Phe Ile His Asn Thr 135 Glu</td><td>Gly Val 40 Ala Gln Thx Lys Gly 120 Lys</td><td>Asn 25 Glu His Pro Glu Gln 105 Glu Ala</td><td>10 Gly Cys Cys Arg Tyr 90 Asp Cys Ala Glu Lys</td><td>Tyr Tyr Ser Gly 75 Cys Gly Lys Gly Lys Lys</td><td>Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140 Gly</td><td>Glu 45 Gly Glu Gly Ala Arg 125 Asp</td><td>Ala 30 Cys Pro Cys Asp Cys 110 Asp Lys</td><td>15 Gly Cys Cys Arg Ser 95 Asn Asn Phe Gly Cys</td><td>Glu Lys Cys Asp S0 Gly Gln Gln Cys Lys Lys</td></a0>	po Glu Ser Cys 50 Ass Val Cys Gln Gln Glu	Thr Thr Asp 35 Ser Thr Asn Pro Gly 115 Tyr Lys	Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg Ile Leu	Thr S Thr Gly Ser Cys 85 Asn Cys Trp Asn Trp	Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thr	Cys His Gly 55 Phe Ile His Asn Thr 135 Glu	Gly Val 40 Ala Gln Thx Lys Gly 120 Lys	Asn 25 Glu His Pro Glu Gln 105 Glu Ala	10 Gly Cys Cys Arg Tyr 90 Asp Cys Ala Glu Lys	Tyr Tyr Ser Gly 75 Cys Gly Lys Gly Lys Lys	Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140 Gly	Glu 45 Gly Glu Gly Ala Arg 125 Asp	Ala 30 Cys Pro Cys Asp Cys 110 Asp Lys	15 Gly Cys Cys Arg Ser 95 Asn Asn Phe Gly Cys	Glu Lys Cys Asp S0 Gly Gln Gln Cys Lys Lys
35 40	<a0 by="" control="" determined="" of="" td="" the="" the<=""><td>po Ser Cya Cya 50 Assa Cya Gin 130 Gin 130 Gin 130</td><td>8 Thr Thr Lap 35 Ser Thr Asn Pro Oly 115 Tyr Lys Asp</td><td>Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg Ile Leu Arg</td><td>Thr S Thr Gly Ser Cys 85 Asu Cys Trp Asu</td><td>Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thr 150</td><td>Cys His Gly 55 Phe Ile His Asn Thr 135 Glu</td><td>Gly Val 40 Ala Gln Thx Lys Gly 120 Lys Gly</td><td>Asm 25 Glu His Pro Glu 105 Glu Ala Thr Ser Arg</td><td>10 Gly Cys Cys Arg Tyr 96 Asp Cys Ala Glu Lys 176</td><td>Tyr Tyr Ser Gly 75 Cys Gly Lys Gly Lys 155 His</td><td>Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140 Gly Asp</td><td>Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp Asn Val</td><td>Ala 30 Cys Pro Cys Asp Cys 110 Asp Lys Cys Cys</td><td>15 Gly Cys Cys Arg Ser 95 Asn Asn Phe Gly Cys</td><td>Cys Cys Asp 80 Gly Gln Gln Cys Lys 160 Gly</td></a0>	po Ser Cya Cya 50 Assa Cya Gin 130 Gin 130 Gin 130	8 Thr Thr Lap 35 Ser Thr Asn Pro Oly 115 Tyr Lys Asp	Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg Ile Leu Arg	Thr S Thr Gly Ser Cys 85 Asu Cys Trp Asu	Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thr 150	Cys His Gly 55 Phe Ile His Asn Thr 135 Glu	Gly Val 40 Ala Gln Thx Lys Gly 120 Lys Gly	Asm 25 Glu His Pro Glu 105 Glu Ala Thr Ser Arg	10 Gly Cys Cys Arg Tyr 96 Asp Cys Ala Glu Lys 176	Tyr Tyr Ser Gly 75 Cys Gly Lys Gly Lys 155 His	Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140 Gly Asp	Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp Asn Val	Ala 30 Cys Pro Cys Asp Cys 110 Asp Lys Cys Cys	15 Gly Cys Cys Arg Ser 95 Asn Asn Phe Gly Cys	Cys Cys Asp 80 Gly Gln Gln Cys Lys 160 Gly
35 40 45	<400 Meet 2 cly Glu Lys Asn 65 Ala Gln Asn Cys Tyr 145 Asp Phe	po Ser Cys Sor Cys So Ass Val Cys Gln Gln Gly Leu	8 Thr Thr Asp 35 Ser Thr Asn Pro Gly 116 Tyr Lys Asp Leu	Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg Ile Leu Arg Cys 180	Thr S Thr Gly Ser Cys 85 Ast Cys Trp Asn Trp 165 Thr	Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thr 150 (1e	Cys His Gly 55 Phe Ile His Asn Thr 135 Glu Gln Leu	Gly Val 40 Ala Gln Thr Lys Gly 120 Lys Gly Cys Thr	Asm 25 Glu His Pro Glu Gln 105 Glu Ala Thr Ser Arg	10 Gly Cys Cys Arg Tyr 90 Asp Cys Ala Glu Lys 170 Ala	Tyr  Tyr  Ser  Gly  75  Cys  Gly  Lys  Lys  155  His	Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140 Gly Asp	Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp Asn Val	Ala 30 Cys Pro Cys Asp Cys 110 Asp Lys Cys Phe Gly 150	15 Gly Cys Cys Arg Ser 95 Asn Asn Phe Gly Cys 175 Gln	Cys Asp 80 Gly Gln Gln Cys Lys Lys Gly Lys Lys Lys Lys Lys Lys
35 40 45	<400 Meet 2 cly Glu Lys Asn 65 Ala Gln Asn Cys Tyr 145 Asp Phe	po Ser Cys Sor Cys So Ass Val Cys Gln Gln Gly Leu	8 Thr Thr Asp 35 Ser Thr Asn Pro Gly 116 Tyr Lys Asp Leu	Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg Ile Leu Arg Cys 180	Thr S Thr Gly Ser Cys 85 Ast Cys Trp Asn Trp 165 Thr	Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thr 150 (1e	Cys His Gly 55 Phe Ile His Asn Thr 135 Glu Gln Leu	Gly Val 40 Ala Gln Thx Lys Gly 120 Lys Gly Cys Thr Ser	Asm 25 Glu His Pro Glu Gln 105 Glu Ala Thr Ser Arg	10 Gly Cys Cys Arg Tyr 90 Asp Cys Ala Glu Lys 170 Ala	Tyr  Tyr  Ser  Gly  75  Cys  Gly  Lys  Lys  155  His	Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140 Gly Asp	Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp Asn Val Tle Gly	Ala 30 Cys Pro Cys Asp Cys 110 Asp Lys Cys Phe Gly 150	15 Gly Cys Cys Arg Ser 95 Asn Asn Phe Gly Cys 175 Gln	Cys Asp 80 Gly Gln Gln Cys Lys Lys Gly Lys Lys Lys Lys Lys Lys
35 40 45	<a0 c<="" color="" of="" td="" the=""><td>po Glu Glu Ser Cys 50 Ass Val Cys Gln Glu Glu Gly</td><td>8 Thr Thr Asp 35 Ser Thr Asn Pro Gly 115 Tyr Lys Asp Leu Glu 195</td><td>Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg Ile Leu Arg Cys 180 Ile</td><td>Thr S Thr Gly Ser Cys 85 Asn Cys Trp 165 Thr Ile</td><td>Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thr 150 11e Asn Pro</td><td>Cys His Gly 55 Phe Ile His Asn Thr 135 Glu Gln Leu Thr</td><td>Gly Val 40 Ala Gln Thr Lys Gly 120 Lys Gly Cys Thr</td><td>Asm 25 Glu His Pro Glu Gln 105 Glu Ala Thr Ser Arg 185 Phe</td><td>10 Gly Cys Cys Arg Tyr 96 Asp Cys Ala Glu Lys 176 Ala Tyr</td><td>Tyr Tyr Ser Gly 75 Cys Gly Lys Gly Lys His</td><td>Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140 Gly Asp Gln</td><td>Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp Asn Val Tle Gly 205</td><td>Ala 30 Cys Pro Cys Asp Cys 110 Asp Lys Cys Phe Gly 190 Arg</td><td>Cys Cys Cys Arg Ser 95 Asn Asn Cys 175 Gin Val</td><td>Cys Asp S0 Gly Gln Gln Cys Lys 160 Gly Leu Ile</td></a0>	po Glu Glu Ser Cys 50 Ass Val Cys Gln Glu Glu Gly	8 Thr Thr Asp 35 Ser Thr Asn Pro Gly 115 Tyr Lys Asp Leu Glu 195	Asp Gly 20 Cys Leu Ser Glu Pro 100 Arg Ile Leu Arg Cys 180 Ile	Thr S Thr Gly Ser Cys 85 Asn Cys Trp 165 Thr Ile	Ser Phe Asn Leu 70 Asp Leu Tyr Gly Thr 150 11e Asn Pro	Cys His Gly 55 Phe Ile His Asn Thr 135 Glu Gln Leu Thr	Gly Val 40 Ala Gln Thr Lys Gly 120 Lys Gly Cys Thr	Asm 25 Glu His Pro Glu Gln 105 Glu Ala Thr Ser Arg 185 Phe	10 Gly Cys Cys Arg Tyr 96 Asp Cys Ala Glu Lys 176 Ala Tyr	Tyr Tyr Ser Gly 75 Cys Gly Lys Gly Lys His	Val Gly Asp 60 Tyr Thr Tyr Ala Ser 140 Gly Asp Gln	Glu Leu 45 Gly Glu Gly Ala Arg 125 Asp Asn Val Tle Gly 205	Ala 30 Cys Pro Cys Asp Cys 110 Asp Lys Cys Phe Gly 190 Arg	Cys Cys Cys Arg Ser 95 Asn Asn Cys 175 Gin Val	Cys Asp S0 Gly Gln Gln Cys Lys 160 Gly Leu Ile

Tyr Val Glu Asp Gly Thr Pro Cys Gly Pro Ser Met Met Cys Leu Asp 230 235 Arg Lys Cys Leu Gln Ilc Gln Ala Leu Asn Met Ser Ser Cys Pro Leu 250 245 Asp Ser Lys Gly Lys Val Cys Ser Gly His Gly Val Cys Ser Asn Glu 260 265 Ala Thr Cys Ile Cys Asp Phe Thr Trp Ala Gly Thr Asp Cys Ser Ile 275 280 10 Arg Asp Pro Val Arg Ass Leu His Pro Pro Lys Asp Glu Gly Pro Lys 290 295 300 Gly Pro Ser Ala Thr Asn Arg Ser Cys Asp Lys Thr His Thr Cys Pro 310 315 Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe 325 330 Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val 340 345 3.50 Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe 355 360 365 Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro 20 375 380 Arg Glu Glu Gln Tyr Aen Ser Thr Tyr Arg Val Val Ser Val Leu Thr 390 395 Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val. 465 410 Ser Ash Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala 26 420 425 tys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg 440 445 Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly 455 460 30 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asm Gly Gln Pro 470 475 Glu Asn Asn Tyr Lya Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser 485 490 Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln 500 505 36 Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His 515 520 525 Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 530 535 30 <210> 19 <211> 3 <212> PRT <213> Artificial Sequence 46 <223> Description of Artificial Sequence: Consensus binding motif <400> 19 Arg Gly Asp zo <220> 20 <211> 67 <212> PRT <213> Artificial Sequence

	<226>
	<223> Description of Artificial Sequence: consensus
	disintegrin domain
5	•
5	<220>
	<221> VARIANT
	<222> 15)(9)
	<223> 3-5 varying residues in a consensus sequence
10	<2270>
	<221> VARIANT
	<222> (11).,(16)
	<223> 3-6 varying residues in a consensus sequence
	<220>
15	<221> VARIANT
	<222> (29) (22)
	<223> 2-4 varying residues in a consensus sequence
	c2205
207	<221> VARIANT
	<222> (24)(30)
	<223> 7 varying residues in a consensus sequence
	<220>
	<221> VARIANT
25	<222> (32)(37)
	<223> 4-5 varying residues in a consensus sequence
	<220>
SIC	<221> VARIANT
30	<222> (40)(43)
	<223> 2-4 varying residues in a consensus sequence
	<320>
	<221> VARIANT
96	<222> (45)(52)
10	<223> 8 varying residues in a consensus sequence
	<220>
	<2205 <221> VARIANT
10	<222> (54)(60)
***	<223> 5-7 varying residues in a consensus sequence
	<220>
	<221> VARIANT
	<222> (52)(66)
45	<223> 3-5 varying residues in a consensus sequence
	<400> 20
	Cys Asp Cys Gly Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
	Cys Map Cys Giy Xoa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xa
sø.	Cys Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
	20 25 30
	Xaa Xaa Xaa Xaa Xaa Cys Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
	35 40 45
35	
	Xaa kaa kaa Cys kaa kas kaa kaa kaa kaa kaa Cys kaa kaa kaa

	50	55	60	
5	Xaa Yaa Cys 68			
1Ġ	<210> 21 <211> 1725 <212> DWA <213> Artificial S	equence		
15	polypeptide	of Artificial Sequenc	ce: fusion	
	<220> <221> CDS <222> (118)(1704) <400> 21	)		
30	gggttttecc agtcacg		cagtg aattgtaata cyac	
			ogacc caagetggct ageca	
25	Met Glu Thr Asp Th	r Leu Leu Leu Trp Val	-	Pro
300	ggt too act ggt ac Gly Ser Thr Gly Th 20	t agt tgt ggg aat gg r Ser Cys Gly Asn Gl; 25	t gtg gtt gaa gaa gga y Val Val Glu Glu Gly 30	gaa 213 Glu
	gag tgt gac tgt gg Glu Cys Asp Cys Gl 35	a cct tta aag cat tg: y Pro Leu Lys His Cy: 40	t gos saa gat oce tgo s Ala Lys Asp Pro Cys 45	tgt 261 Cys
35	Leu Ser Asn Cys Th: 50	r Leu Thr Asp Gly Sei 55	t act tgt gct tit ggg r Thr Cys Ala Phe Gly 60	Leu
40	tgt tgc asa gac tg: Cys Cys Lys Asp Cy: 65	c sag tto cta cca to: s Lys Phe Leu Pro Se: 70	a ggg aaa gtg tgt aga r Gly Lys Val Cys Arg 75	aag 357 Lys 80
	gağ gir ast gaz tgi Glu Val Asn Glu Cyi 8	s Asp Leu Pro Glu Tr	g tgc aat ggt act tcc p Cys Asn Gly Thr Sex 0 95	cat 405 His
45	Lys Cys Pro Asp Asp 100	p Phe Tyr Val Glu Ası 105	t ggs att ccc tgt aag p Gly Ile Pro Cys Lys 110	Glu
30	Arg Gly Tyr Cys Ty: 115	r Glu Lys Ser Cys His 120	t gac cgc aat gaa cag s Asp Arg Asn Glu Gln 125	Cya
	agg agg att tit gg: Arg Arg Ile Phe Gly 130	t goa ggd goa aat act y Ala Gly Ala Asn Tha 135	t goa agt gag act tge K Ala Ser Glu Thr Cys 140	tac 549 Tyr
55	ada gad ttg dac acr	c the ggt gad ogt gtt	t ggt cac tgt ggt atc	aaa 597

	Lys 145	Gla	Leu	Asn	Thr	Leu 150	Gly	Asp	Arg	Val	G1y 155	His	Cys	Gly	Ile	150	
5				tat Tyr													645
10				gag Glu 180													593
fá				tgg Trp													741
ıa				999 Gly													789
20				01Å 888													837
25				ttg Leu													885
	gge	atc	tgc	aac	aac	aaa	cat	cac	tge	cat	tgc	aat	tat	ctg	ugg	gac	933
30	GIY	Tle	Cys	Asn 260	Asn	Lys	His	His	Сув 265	His	Cys	Asn	Tyr	Leu 270	Trp	Asp	
				tge Cys													981
35	1629	•		aag													
	Pro	290	Pro	Lys	Arg	Lys	Lys 295	Lys	Lys	Lys	Arg	Ser 300	Cys	Asp	Lys	Thr	
49	1077	7		cca													
	H18 305	Thr	Cys	Pro	Pro	Cys 310	Fro	Ala	Pro	Glu	Ala 315	Glu	Gly	Ala	Pro	320	
45	1125	3		ttc													
	Val	Phe	Leu	Phe	Pro 325	Pro	Lys	Pro	Lys	330	Thr	Leu	Met	Ile	Ser 335	Arg	
50	acc 1173		gag	gtc	aca	tgc	gtg	gtg	gtg	gac	gtg	age	cac	gaa	gac	ect	
<i>30</i>	Thr	Pro	Glu	740	Thr	Суя	Val	Va.l	Val 345	Asp	Val	Ser	Hís	Glu 350	Asp	Pro	
	1221	L		tte													
55	Glu	Val	Lys 355	Phe	Asn	Trp	Tyr	Val 360	Asp	Gly	Val	Glu	Val 365	Kis	Asn	Ala	

	aag aca	889	ccg	<b>c</b> 99	393	gag	cag	tac	aac	age	acg	tac	cgg	gtg	gtc
	1269 Lys Thr	Long	Yearan	N 2000	27.0	e)	77.	Minis		Cara	001 to an	<i>m</i> , 110		x	ex. 2
	370	cys	820	wrā	CSLIL	375	nae	ryr	PASTS	sex	380	tyr	arg	Val	Val
5															
	ago gto	ctc	acc	gro	ccs	cac	cag	gac	tgg	ctg	aat	ggc	aag	gag	tac
	1317 Ser Val	fan	mina	1/57	Y 000	171 0	O		Thomas	Y	A	0244		<b>~</b> 2	m
	335	TAGS PT	2.942.	A 65 %	390	47.3	024	Mag	TED	395	Ass	GIY	rys	GLU	400
10															
	aag tgc	283	gre	tee	aac	222	gcc	ctc	cca	gcc	cee	atc	gag	asa	acc
	1365 Lys Cys	Lve	Val	Ser	A.on	Tare	616	Lans	Pro	230	Down	rle	o.i.o	Lne	fffile sv
		,.		405	74074	37.3	A44	AIC U	410	Nan	6.0	246	010	415	ALLA
15															
	atc tcc 1433	aaa	gcc	aaa	333	cag	ccc	cga	gaa	cca	cag	gtg	tac	acc	ctg
	Ile Ser	Lys	Ala	Lys	Gly	Gln	Pro	Ara	Glu	Pro	Gln	Val.	TVY	Thr	Len
			420					425					430		
20	ccc cca 1451	ree	c99	gat	gag	erg	acc	aag	aac	cag	gtc	agc	ctg	acc	tgc
	Pro Pro	Sex	Arg	asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
		435					440					445			
	etg gre	aaa	gac	tite	tat	can	apr	osc.	ate	acr	nto	0.8/3	tran	man	200
25	1509														-
	Leu Val	Lys	Gly	Phe	Tyr		Ser	Asp	Ile	Ala		Glu	Trp	Glu	Ser
	4.50					455					460				
	aat ggg	cag	ecg	gag	aac	aac	tac	aag	acc	acg	cet	ccc	gtg	etg	gac
36	1557		_												
	Asn Gly 465	GIR	Pro	wiu	470	asn	TYX	TAR	Tar	475	Pro	Pro	Val	Leu	A80
															****
	tcc gac	gg¢	tcc	ttc	ttc	ote	tac	agc	aag	ctc	acc	gtg	gac	aag	agc
35	Ser Asp	G3 v	Ser	Dho	Dhe	7.011	Where	Car	1.20	Lens	The	On I	nan.	Yair	dex
				485			-7-	0.54	490	200	****	***	- mig	495	1701
	agg tgg 1653	cag	cag	999	aac	gte	tte	cca	rge	toc	gtg	atg	cat	gag	get
40	Arg Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
40			500					505					510		
	ctg cac	227	rac	rac	200	020	220	200	200	+00	atra	n nh	~~~	ank	
	1701						u.u.g				~~9		ccg	33"	crecia
	Leu Ris	Asn	His	Tyr	Thr	Gin		Ser	Lèu	Ser	Leu		Pro	Gly	Lys
48		515					520					525			
	tga act:	gage	99 (	rege	cacag	ga t									
	1725														
50	<210> 23	2													
	<211> 5														
	<21.2> 91		-4-1												
	<223> At	CILI	CAA.	. See	รักธมเ	ce									
55	<220>														
_	<223> De	escri	ptic	on of	E Art	tifíc	cial	Seq	zence	t: fi	sion	9			

polypeptide

```
<400> 22
          Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Trp Val Pro
                                            3.8
           Gly Ser Thr Sly Thr Ser Cys Gly Asn Gly Val Val Glu Glu Gly Glu
                      20
                                        25
           Glu Cys Asp Cys Gly Pro Leu Lys His Cys Ala Lys Asp Pro Cys Cys
                                   40
           Leu Ser Asn Cys Thr Leu Thr Asp Gly Ser Thr Cys Ala Phe Gly Leu
                             55
                                                  60
           Cys Cys Lys Asp Cys Lys Phe Leu Pro Ser Gly Lys Val Cys Arg Lys
                            70
                                            75
           Glu Val Asn Glu Cys Asp Lea Pro Glu Trp Cys Asn Gly Thr Ser His
                         85
                                          95
           Lys Cys Pro Asp Asp Fhe Tyr Val Glu Asp Gly Ile Pro Cys Lys Glu
                     200
                                    1.05
                                                        110
           Arg Gly Tyr Cys Tyr Glu Lys Ser Cys His Asp Arg Asn Glu Gln Cys
                                   120
           Arg Arg Ile Phe Gly Ala Gly Ala Asn Thr Ala Ser Glu Thr Cya Tyr
                              135
20
          Lys Glu Leu Ann Thr Leu Gly Asp Arg Val Gly Ris Cys Gly Ile Lys
                    150
                                        155
           Asn Ala Thr Tyr Ile Lys Cys Asn Ile Ser Asp Val Gln Cys Gly Arg
                                 170
                        265
           Ile Gln Cys Glu Asn Val Thr Glu Ile Pro Asn Met Ser Asp His Thr
26
                     1.80
                                      185
           Thr Val His Trp Ala Arg Phe Asn Asp Ile Met Cys Trp Ser Thr Asp
                  195
                                  200
                                                      205
           Tyr His Leu Gly Met Lys Gly Pro Asp Ile Gly Glu Val Lys Asp Gly
                               215
                                                 220
           Thr Glu Cys Gly Tle Asp His The Cys Tle His Arg His Cys Val His
                           239
                                     235
           The Thr Ile Leu Asn Ser Asn Cys Ser Pro Ala Phe Cys Asn Lys Arg
                         245
                                         250
                                                          255
           Gly Ile Cys Asn Asn bys His His Cys His Cys Asn Tyr Leu Trp Asp
                     260
                                      265
35
           Pro Pro Asn Cys Leu Ile Lys Gly Tyr Gly Gly Ser Val Asp Ser Gly
                275
                                   280
                                                     285
           Pro Pro Pro Lys Arg Lys Lys Lys Lys Lys Arg Ser Cys Asp Lys Thr
                               295
                                                  300
           His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser
                          310
                                     . 335
           Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met 11e Ser Arg
325 330 335
           Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
                      340
                                       345
           Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
                                   360
                                            365
           Lys Thr Lys Pro Arg Glu Glu Glo Tyr Asn Ser Thr Tyr Arg Val Val
                                375
                                                  386
           Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
                            390
                                               395
           Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                        405
                                          410
           The Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
                     420 425
                                                       430
           Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
                                            445
                 435 440
           Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
                                455
                                                  460
```

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp 470 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser 485 4.90 Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala 500 505 510 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 515 528 525

Claims

203

25

48

40

26

60

55

- 1. A method of antagonizing the binding of an integrin to its ligands comprising contacting a cell that expresses the integrin with an effective amount of an ADAM disintegrin domain polypeptide.
  - 2. A method of antagonizing the binding of an integrin to its ligands in a mammal in need of such treatment comprising administering an effective amount of an ADAM disintegrin domain polypeptide.
  - 3. The method of claim 2 wherein the mammal is afflicted with a condition selected from the group consisting of ocular disorders, malignant and metastatic conditions, inflammatory diseases, estecporosis and other conditions mediated by appeterated bone respiration, restenosis, inappropriate platetet activation, recruitment, or appreciation, thrombosis, or a condition requiring tissue repair or wound healing.
  - 4. A method of inhibiting andiogenesis in a mammal in peed of such treatment, comprising administering to the mammal an inhibition-effective amount of an ADAM disintegrin domain polypectide, wherein the disintegrin domain does not contain an RGD sequence.
- 5. The method of one of claims 1-4 wherein the ADAM disintegrin domain is in the form of a multimer.
  - 6. The method of claim 5 wherein the multimer is a dimer or trimer.
  - 7. The mathod of claim 5 wherein the multimer comprises an Fc polypeptide or a leucine zipper.
  - 8. The method of one of claims 1-7 wherein the ADAM disintegrin domain is from a human ADAM.
  - 9. The method of claim 8 wherein the ADAM disintegrin domain is from an ADAM selected from the group consisting of ADAM-8, ADAM-9, ADAM-10, ADAM-15, ADAM-17, ADAM-20, ADAM-21, ADAM-22, ADAM-23, and ADAM-29,
  - 10. The method of claim 9 wherein the ADAM disintegrin domain is from ADAM-17. ADAM-20, or ADAM-23.
  - 11. The method of one of claims 1-10 wherein the ADAM disintegrin domain polypeptide comprises an amino acid sequence selected from the group consisting of:

(a) amino acids 1-494 of SEQ ID NO:2, amino acids 23-284 of SEQ ID NO:2, amino acids 1-539 of SEQ ID NO:4, amino acids 29-303 of SEQ ID NO:4, amino acids 1-465 of SEQ ID NO:6, amino acids 29-295 of SEQ ID NO:6, amino acids 1-622 of SEQ ID NO:8, amino acids 23-292 of SEQ ID NO:8, amino acids 1-446 of SEQ ID NO:10, amino acids 23-216 of SEQ ID NO:10, amino acids 1-535 of SEQ ID NO:12, amino acids 23-305 of SEQ ID NO: 12, amino acids 1-529 of SEQ ID NO:14, amino acids 23-299 of SEQ ID NO:14, amino acids 1-542. of SEQ ID NO:16, amino acids 23-312 of SEQ ID NO:16, amino acids 1-540 of SEQ ID NO:18, amino acids 28-310 of SEQ ID NO:18, smine acids 1-528 of SEQ ID NO:22, amine acids 23-298 of SEQ ID NO:22; (b) fragments of the polypeptides of (a) wherein said fragments retain at least one ADAMdis activity;

- (c) variants of the polypeptides of (a) or (b), wherein said variants retain at least one ADAMdis activity; and (d) fusion polypeptides comprising the polypeptides of (a), (b), or (c), wherein said fusion polypeptides retain at least one ADAMdis activity.
- 12. The method of claim 1.1 wherein the ADAM disintegrin domain comprises an amino acid sequence selected from

the group consisting of amino acids 34-91 of SEQ ID NO:2, 34-92 of SEQ ID NO:4, 34-99 of SEQ ID NO:6. 34-92 of SEQ ID NO:6. 34-92 of SEQ ID NO: 14, 34-91 of SEQ ID NO: 14, 34-92 of SEQ ID NO: 18, 34-91 of SEQ ID NO: 14, 34-92 of SEQ ID NO: 18, 34-91 of SEQ ID NO: 14, 34-92 of SEQ ID NO:

 The method of one of claims 1-12 wherein the ADAM disintegrin domain polypeptide is a variant that is at least 70%, 80%, 90%, 95%, 98%, or 99% identical in amino acid sequence to a polypeptide selected from the group consisting of:

(a) amino acids 1-494 of SEQ ID NO?s, amino acids 23-264 of SEQ ID NO2, amino acids 1-533 of SEQ ID NO4, amino acids 28-300 of SEQ ID NO3, amino acids 2-525 of SEQ ID NO3, amino acids 29-256 of SEQ ID NO3, amino acids 29-256 of SEQ ID NO3, amino acids 1-448 of SEQ ID NO3, amino acids 1-448 of SEQ ID NO3, amino acids 29-305 of SEQ ID NO3, amino

wherein said variant polypeptide retains at least one ADAMdis activity.

15

55

14. The method of one of claims 1-10 wherein the ADAM disintegrin domain polypeptide is encoded by a nucleic acid comprising a sequence selected from the group consisting of:

(a) nucleatidas 118-1599 of SEQ ID NO:1, nucleatidas 184-909 of SEQ ID NO:1, nucleatidas 46-1644 of SEQ ID NO:3, nucleatidas 112-2644 of SEQ ID NO:3, nucleatidas 25-1419 of SEQ ID NO:5, nucleatidas 19-779 of SEQ ID NO:5, nucleatidas 19-779 of SEQ ID NO:5, nucleatidas 19-780 of SEQ ID NO:1, nucleatidas 19-780 of SEQ ID NO:1, nucleatidas 19-780 of SEQ ID NO:1, nucleatidas 19-80 of SEQ ID NO:1, nucleatidas 19-80 of SEQ ID NO:1, nucleatidas 19-80 of SEQ ID NO:11, nucleatidas 19-90 of SEQ ID NO:11, nucleatidas 19-90 of SEQ ID NO:15, nucleatidas 25-1644 of SEQ ID NO:15, nucleatidas 25-1640 of SEQ ID NO:15, nucleatidas 19-90 of SEQ ID NO:21, nuc

- 30 (b) sequences which, due to the degeneracy of the genetic code, encode a polypeptide encoded by a nucleic acid of (a); and
  - (c) sequences that hybridize under conditions of moderate or high stringency to a sequence of (a) or (b) and that encode a polypeptide that ratains at least one ADAMdis activity.
- 35 15. The method of one of claim 11-14 wherein the ADAMdis activity is selected from the group consisting of integrin birtiding activity, inhibition of endothetial cell migration, and inhibition of angiogenesis.
  - 16. The method of one of claims 1-15 wherein the ADAM disintegrin domain polypeptide has been produced by culturing a recombinant cell that encodes the ADAM disintegrin domain polypeptide under conditions permitting expression of the ADAM disintegrin or oneant polypeptide, and recovering the ADAM disintegrin domain polyperptide.
  - 17. The method of one of claims 1-16 wherein the ADAM disintegrin domain polypeptide is present in a composition comprising a pharmaceutically acceptable carrier.
- 45 18. The method of claim 2 wherein the mammal has a disease or condition mediated by angiogenesis.
  - 19. The method of claim 18 wherein the disease or condition is characterized by ocular recovercularization.
- The method of claim 18 wherein the disease or condition is a solid tumor.
  - 21. The method of one of claims 1-20 wherein the method further comprises treating the mammal with radiation.
  - The method of one of claims 1-21 wherein the method further comprises treating the mammal with a second therapeutic agent.
  - 23. The method of claim 22 wherein the second therapeutic agent is selected from the group consisting of alkylating agents, artimetabolises, vinca alkaloids and other plant-derived chemotherapeutics, artitumor antibiotics, artitumor enzymes, toposemerase inhibitors, platinum analogs, adrenocortical suppressants, hormones and artitimorpores.

antibodies, immunotherapeutics, radiotherapeutics, and biological response modifiers.

- 24. The method of claim 22 wherein the second therapeutic agent it selected from the group consisting of esplatin, cyclophosphamids, bleenywin, carboplatin, fluorounali, 5-fluorounali, 5-fluorounayuridine, methotrexeet, lexcl. asparaginase, vincriatine, vinblastine, mechioretamine, melphalan, 5-fluorounavyuridine, lymphoximes and cytokines such as interflexibins, interferone (alpha, beta, or della), and TNF, chlorambucil, busuffan, carmostine, lomustine, semistines, is retrotroom, dicaratrazine, cytambine, mercaptorine, finoguenine, vindesine, etoposidie, teriploside, dactinonypin, disunorubión, doxorubión, bleomycin, pilicamycin, mitomycin, claunorubión, doxorubión, bleomycin, claunorubión, como control della production della production.
  - 25. The method of claim 22 wherein the second therapeutic agent is a polypeptide, including soluble forms thenot, selected from the group consisting of Ri3 ligand, CD40 ligand, interleukin 26, Interleukin 24, eHB8 ligand, anti-4-BB antibodies, TRAIL, TNF entagonists and TWEAX-R encaponists unduling TMFAFF, Tek antagonists, TWEAK antagonists and TWEAX-R entagonists including TMFAFF, VEGF entagonists including anti-VEGF antibodies, VEGF receptor entagonists, CD 148 binding proteins, and needing-3 antagonists.
  - 26. The method of claim 2 wherein the ADAM disintegrin domain is administered parenterally.

15

25

un

80

- A mathod for inhibiting the biological activity of an integrin selected from the group consisting of α_iβ₁, α_iβ₁, α_iβ₂, α_iβ₃, α_iβ₄.
   α_iβ₁, α_iβ₄, α_iβ₄, α_iβ₄.
   α_iβ₁, α_iβ₄, α_iβ₄.
   α_iβ₁, α_iβ₄.
   α_iβ₁, α_iβ₄.
   α_iβ₁, α_iβ₄.
   α_iβ₁.
   α_iβ₁.
  - 26. The method of claim 27 wherein the integrin is α_iβ₃ and wherein the ADAM disintegrin domain does not contain an RGD sequence.
  - 29. The method of claim 28 wherein the ADAM is ADAM-17, ADAM-20, or ADAM-22.
  - 30. The method of claim 27 wherein the integrin is rx.8, and the ADAM is ADAM-23.
- 31. The method of claim 27 wherein the integrin is α₆β₁ and the ADAM is ADAM-15 ADAM-21, ADAM-22, or ADAM-23.
  - The method of claim 27 wherein the integrin is α₆β₁ or α₆β₄ and the ADAM is ADAM-10, ADAM-17, ADAM-22, or ADAM-23.
  - 5 33. The method of claim 27 wherein the Integrin is ε_Lβ₅ and the ADAM is ADAM-10, ADAM-15, or ADAM-23.
    - 34. A method for identifying a compound that modulates integrin biological activity comprising:
      - (a) combining a test compound with an integrin and an ADAM disintegrin domain polypeptide that binds to the integrin; and
      - (b) determining whether the test compound afters the binding of the ADAM disintegrin domain polypeptide to the integrin.
- 35. A method for identifying a compound that modulates the interaction between an integrin and an ADAM disintegrin domain comprising;
  - (a) combining a test compound with the integrin and an ADAM disintegrin domain polypeptide that binds to the integrin; and
  - (b) determining whether the test compound eiters the binding of the ADAM disintegrin domain polypeptide to the integrin.
  - 36. The method of claim 34 or 35 wherein the integrin is present on a cell surface.
  - 37. The method of claim 36 wherein the cell is an endothelial cell.
    - The method of one of claims 34-37 wherein the integrin is selected from the group consisting of α_sβ₃, α₂β₁, α₅β₄,
       α₆β₁, α₆β₄, and α₆β₆.

- 39. The method of one of claims 34-38 wherein the Integrin biological activity or integrin binding activity is at least partially inhibited.
- 49. A method for identifying a compound that inhibits endothelial cell migration and/or angiogenesis comprising:

10

90

25

30

35

40

as

50

- (a) combining a test compound with endothelial cells and with an ADAM disintegrin domain polypeptide that binds to endothelial cells; and
- (b) determining whether the test compound alters the binding of the ADAM disintegrin domain polypeptide to the endothelial calls.
- The method of one of claims 34-40 wherein the ADAM disintegrin domain polypeptide comprises an ADAM disintegrin domain from ADAM-8, ADAM-9, ADAM-10, ADAM-15, ADAM-17, ADAM-20, ADAM-21, ADAM-22, ADAM-23, or ADAM-28.
- 42. The method of claim 41 wherein the ADAM disintegrin domain polypeptide comprises an ADAM disintegrin domain from ADAM-17, ADAM-20, or ADAM-23.



European Patent Office

### PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 66 82 6259 shall be considered, for the purposes of subsequent proceedings, as the European search report

		ERED TO BE RELEVANT disation, where appropriate.	Fletevant	A. 4000000 2 2000 00 20 10
Casegory	Okation of document with in of relevant passa		Fielevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	SCHLUESENER HERMANN domain of ADAM 8 en against rat experim encephalomyelitis, a polyvalent autoan JOURNAL OF NEUROIMM vol. 87, no. 1-2.	J: "The disintegrin hances protection ental autoimmune neuritis and uveitis by tigen vaccine." UNDLOGY, 7-01), pages 197-202,	1-3.16, 17,26	TRU: (1219)/64 C1219/64 C1219/5/5 A61/63/5 A61/63/7 A61/6
				SEARCHED (IPC)
				C07K C12N
The Search and serviced Chairns ser Chairn	PPLETE SEARCH  TO REGISTER THE THE PROPERTY AND THE PROPE	oppleaders, or one of more of the sleating, doesn't be a sleat of the sleat of the sleat of the sit on the sleat ordinary.	io nuci	
	Pleas of streeth	Date of correlation of the beauth		Extendent
	Page of assecth Berlin	Date of correlation of the seconds 23 May 2007	De	Boombon Kok, Ad
X parti Y parti	1	23 May 2907  Y: theory or process E: serifer patent cou-	uncertying the o ment, but public the speciment on	Kok, Ad



European Pater

# PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 06 02 6259

	DOCUMENTS CONSIDERED TO BE RELEVANT	CLASSIFICATION OF THE APPLICATION (IPC)	
Category	Obstion of document with indication, where appropriate, of relevant passages	Relevant to elsim	······································
Э,Х	NATH DEFPA ET AL: "Interaction of metargidin (ADM-15) with alphawbeta3 and alphabeta1 integrins on different haemopoletic cells." JOURNAL OF CELL SCIENCE, vol. 112, no. 4, February 1999 (1999-02), pages 579-587, XP002186267 LONDON GB ISSN: 0021-9533 the whole document, especially page 586, column 1	1-3, 7-18,27, 31,33-41	
4	CO. (TIME) T	4 35-42	
×	ZHANG XI-PING ET AL: "Specific interaction of the recombinant disintegrin-like domain of MOC-15 (metargidin, ADMM-15) with integrin alphaybeta3." JOURNAL OF 810LOSICAL CHEMISTRY, vol. 273, no. 13, 27 March 198 (1998-83-27), pages 7345-7356, XP002186268 MASHIMSTON B. (1998-83-27), pages 7345-7356, ZP002186268 MASHIMSTON B. (1998-83-27), pages 7349, roll while decument, especially page 7349, column 2, paragraph 2	1-3, 9-18,27, 31,33	TECHNICAL PELIS BE MONTHS (BUC)

and the same and the second of an



# PARTIAL EUROPEAN SEARCH REPORT Application Number

EP 66 62 6259

***********	DOCUMENTS CONSIDERED TO BE RELEVANT	T 22	APPLICATION (IFC)
Category	Otation of document with indication, where appropriate, of relevant passages	Petevant to etains	
¥	SHEU J-P. ET. Al.: "Inhibition of anglogenesis in vitro and in vivo: comparison of the relative activities of triffavin, an Arg-Bly-Asp-containing peptide and anti-alphabeta3 integrin monoclonal anti-body with the second period of the second period perio	4	
Ą	ISELEPIS VICKY H ET Al: "An ReD to LDV motific conversion within the disintegrin ktstrin generates an integrin antagonist ktstrin generates an integrin antagonist receptor specificity: Evidence for tered receptor specificity: Evidence for integrin-binding motifis" JUDNNAL O BROUGSICAL CHEMISTEY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTEY, BALTIMORE, Wol. 272, no. 34, 1997, pages 21341-21348, VSDC2149956 ISSN: 6021-9258 ISSN: 6021-9258	4	TECHNOCAL PIELDS SEARCHED (IPC)
A,D	WO 99/41388 A (IMMUNEX CORP) 19 August 1999 (1999-08-19) * the whole document *	1-42	***************************************
A, C	WO 99/23228 A (IMMUNEX CORP) 14 May 1999 (1999-05-14) * page 6, paragraph 2 * * page 8, paragraph 2 * -/	1-42	



European Pater

# PARTIAL EUROPEAN SEARCH REPORT Application Number

Application Number EP 95 92 6259

	DOCUMENTS CONSIDERED TO BE RELEVANT		CLASSIFICATION OF THE APPLICATION (IPC)
Dasagory	Citation of document with indication, where appropriate, of relevant passages	Fielevant to claim	
D.A	WO 99/36549 A (IMMUNEX CORP) 22 July 1999 (1999-67-22) * page 4, line 24 - line 30 * * page 7, line 25 - page 8, line 26 *	1-42	
Р,Х	WO 00/43493 A (HUMAN GENOME SCIENCES INC) 27 July 2006 (2000-07-27)	1-9, 11-29, 31,32, 34-42	
	* page 13, line 3 * * page 17, line 6 - line 7 * * page 196, line 31 - page 204, line 33 * * page 227 - page 234 * * examples 10,39,41-43,49 *		TECHNICAL PIELDS
Ε	WO 01/74857 A (BRISTOL-MYERS SQUIBB CO) 11 October 2001 (2001-10-11)	1-18,20, 27,28, 30-42	SEARCHED (PC)
	* page 4, line 26 - page 6, line 16 * * page 7, line 11 - page 8, line 26 * * page 14, line 17 - line 34; example 12 *		

100



### INCOMPLETE SEARCH SHEET C

Application Number

EP 06 02 6259

Although claims 2, 4 (and claims dependent thereof) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleade effects of the compound/composition.

Claim(s) searched completely:

Claim(s) searched incompletely: 1-10. 15-42

Reason for the limitation of the search:

Present claims 1-10 and 15-42 relate to a method defined by reference to the use of a compound having a desirable characteristic or property. namely having an "ADAM disintegrating domain". The claims cover all compounds having this characteristic or property. whereas the application provides support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the subject-matter of claims 11-14, insofar as those claims refer to amino acid or nucleotide sequences as identified in the sequence listing since fragments (claim 11b, 13b), variants (claim 11c) fusion proteins (claim 11d) or hybridizing nucleic acids (claim 14 c) retaining at least one 'ADAMdis' activity are not disclosed as well.



Application Number

EP 96 02 6259

CLAIMS INCURRING FEES
The present European patent application comprised at the time of fling more than ten claims.
Only part of the dailins have been paid within the prescribed time limit. The prescrib European search report has been drawn up for the first ten dailins and for those dailins for which elains fees here been paid, namely d
No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first lien datins.
LACK OF UNITY OF INVENTION
The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:
see sheet B
All turther search fees have been paid within the fixed time limit. The present European search report haben drawn up for all claims.
As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
Only part of the further search fees have been paid within the fixed time limit. The present European secon report has been drawn up for those parts of the European patient application which relate to the inventions in respect of which search face have been paid, namely datus.
None of the further search leas have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the citalins, namely disme:



### LACK OF UNITY OF INVENTION SHEET B

Application Number EP 95 92 6259

The Search Division considers that the present European patent application does not comply with the requirements of unity of inventions and relates to several inventions or groups of inventions, namely:

1. claims: 1-3, 18-20, 26 completely and 5-17, 21-25 partly

A method of antagonizing the binding of an integrin to its ligand, in vitro or in vivo, by administering an effective amount of an ADAM disintegrin domain polypeptide

2. claims: 4, 28, 29 completely and 5-17, 21-25, 27 partly

A method of inhibiting angiogenesis in a mammal comprising administering an ADAM disintegrin domain polypeptide which does not contain a RGD sequence

3. claim: 27 partly and 30 completely

A method for inhibiting the biological activity of alphalibetal integrin comprising contacting the integrin with an ADAM-23 disintegrin polypeptide

4. claim: 27 partly and 31 completely

A method for inhibiting the biological activity of alphaVetal integrin comprising contacting the integrin with an ADAM disintegrin polypeptide and the ADAM is ADAM-15, -21, -22 or -23

5. claim: 27 partly and 32 completely

A method for inhibiting the biological activity of alphaVIbetaI or alphaVIbetaIV integrin comprising contacting the integrin with an ADAM disintegrin polypeptide and the ADAM is ADAM-16, -17, -22 or -23

6. claim: 27 partly and 33 completely

A method for inhibiting the biological activity of alphaVbetaV integrin comprising contacting the integrin with an ADAM disintegrin polypeptide and the ADAM is ADAM-18, -15 or -23

7. claims: 34-42

Methods for identifying compounds that modulate integrin biological activity

#### ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO.

EP 96 92 6259

This amery lists the potent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office ECP file on The European Pleten Office is in two way lable for these particulars which are merely given for the purpose of information.

23-65-2087

	Patent document od in search repor		Publication date		Patent family member(s)		Publication date
WO	9941388	A	19~08~1999	AU CA EP JP NZ	751007 3290899 2320422 1954982 2002503472 506817	B2 A A1 A2 T A	68-08-208 30-08-199 19-08-199 29-11-208 65-92-208 29-08-208
WO	9923228	A	14-05-1999	AU AU CA EP JP NZ	749671 1267699 2308110 1027442 2001521742 504431	A Al Al T	04-07-200 24-05-199 14-05-199 16-08-200 13-11-200 28-09-200
WC	9936549	A	22-87-1999	AT AU CA DE DE EP ES JP NZ PT	326496 750038 2221999 2317638 69930376 1945914 1945914 2260839 2002508969 596277 1045914		15-04-200 11-07-200 02-08-199 22-07-199 12-18-200 17-07-200 25-18-200 01-11-200 26-03-200 31-07-200
MO	0943493	A	27-07-2000	AU	3212496	A	07-08-200
WO	0174857	A	11-10-2001	AU CA EP JP	4980201 2405319 1266756 2603529356		15-10-200 11-10-200 02-01-200 07-10-200

CHC 60109

\$ For more details about this arresx , see Official Journal of the European Patent Office, No. 12/82

#### REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only, it does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all flability in this regard.

#### Patent documents cited in the description

- US 18486500 P f00011
- US 5674704 A [0019]
- US 5716805 A [0022]
- WO 0015258 A, Daniel f00231 f00791 US 5554512 A (0026)
- US 5447860 A. Ziegler (0033)
- WO 0075323 A. Cerreiti 100331
- US 5763223 A [0035]
- US 60172878 B f00361
- US 60203347 E [0036]

- WO 9641624 A f00401
- WO 9923228 A f00401
- WO 9936549 A [0040]
- WO 9941388 A [0040] [0040]
- WO 9310161 A [0056] [0056]
- US 5457035 A (0066)
- US 4751180 A [0058]
- US 4935233 A [0058]
- WO 9410308 A [0059]

#### Non-patent literature cited in the description

- WESTCAMP : BLOBEL, Proc. Natl. Acad. Sci. USA. 1994, vol. 91, 2748 (0005) WOLFSBERG et al. Dev. Blot., 1995, vol. 169, 378
- 1000051 1000061 ALFANDARI et al. Dev. Biol., 1997, vol. 182, 314
- fonns1
- WESKAMP et al. Proc. Natl. Acad. Sci. USA, 1994. vol. 91, 2748 f00061 ZHANG et al. J. Biol. Chem., 1998, vol. 273 (13),
- 7345 (0007) NATH et al. J. Cell Science, 1999, vol. 112, 579
- 100073 FOLKMAN: 1971. N. Engl. J. Med., vol. 285, 1182
- FOLKMAN et al. Nature, 1989, vol. 339, 58 [0010]
- KIM et al. Nature, 1993, vol. 362, 841 [0010]
- HORI et al. Cancer Res., 1991, vol. 51, 8180 [0010] ZETTER, Annu. Rev. Med., 1998, vol. 49, 407 [0010]
- BERGERS et al. Science, 1999, vol. 284, 808 [0010]
- Science, 1994, vol. 264, 569 (0011)
- Cell. 1994, vol. 79, 1157 [0011].
- SATOH-HORIKAWA et al. J. Biol. Chem., 2000, vol. 275 (14), 10291 [0031] CHICHEPORTICHE et al. J. Biol. Chem., 1997, vol.
- 272 (51), 32401 [0036] FENG et al. Am. J. Pathol., 2000, vol. 156 (4), 1253.
- Genomics, 1997, vol. 41 (1), 56 [0040]
- J. Cell. Biol., 1996, vol. 132 (4), 717 [9040]
- J. Biol. Chem., 1997, vol. 272 (39), 24588 [0040]
- J. Biol. Chem., 1996, vol. 271 (9), 4593 [0040] Biochem Biophys, Res. Commun., 1999, vol. 263, 810 (0040)
- NEEDLEMAN; WUNSCH, J. Mol. Biol., 1970, vol. 48, 443 (0044)

- . SMITH: WATERMAN, Adv. Appl. Math. 1981, vol. 2 482 [0044]
- DEVEREUX et al. Nucl. Acids Res., 1984, vol. 12. 387 (0044)
- GRIBSKOV: BURGESS, Nucl. Acids Res., 1986. vol. 14, 6745 [0044] Atlas of Protein Sequence and Structure, National
- Biomedical Research Foundation, 1979, 353-358 moaar ASHKENAZI et al. Proc. Nail. Acad. Sci. USA, 1991.
- vol. 88, 10535 [0054] BYRN et al. Nature, 1990, vol. 344, 677 [0054].
- . HOLLENBAUGH : ARUFFO, Construction of Immunoglobulin Fusion Proteins. Current Protocols in Immunalogy, 1992, 10.19,1-10.19,11 [0054]
- BAUM et al. EMBO J., 1994, vol. 13, 3992 [0056]
- LANDSCHULZ et al. Science, 1988, vol. 240, 1759 100691
- NOPPE et al. FEBS Lett., 1994, vol. 344, 191 (0059) FANSLOW et al. Semin. Immunol., 1994, vol. 6, 267 100591
- TAKAHASHI et al. J. Am. Soc. Nephrol., 1999, vol. 10. 2135-45 F00791
- BROWDER; KLEMENT et al. Cancer Research, 2000, vol. 50, 1878 [9080]
- J. Clin. Invest., 2000, vol. 105 (8), R15 [0080]
- BARINAGA, Science, 2000, vol. 288, 245 [0080]
- EMBO J., 1991, vol. 10, 2821 [0084]
- BROOKS et al. Science, 1994, vol. 264, 569 [0088] WANG et al. Mol. Biol. of the Cell. 1998, vol. 9, 865.
- BIODESIGN, A. TE VELDE et al. J. Immunol., 1988. vol. 140, 1548 [0088]
- · PATTARAMALAI et al. Exp. Cell. Res., 1996, vol. 222, 281 [0088]

- SCHLOSSMAN et al. Leukocyte Typing V: White Cell Differntletion Antigens, Oxford University Press, 1995 [0088]
- WEINAKER et al. J. Biol. Chem., 1994, vol. 269, 6940 [0088]
- Molec. Biol. of the Cell, 2000, vol. 11, 1457 [0092]
- MARTIN et al. In Vitro Cell Dev Biol, 1997, vol. 33, 261 [0097]
- KENYON et al, Invest Optnamol. & Visual Science, 1996, vol. 37, 1625 [0101]